STUDIES DIRECTED TOWARDS THE SYNTHESIS OF METAL-CONTAINING KETONES

A thesis submitted to the

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in fulfilment of the requirements for the degree of

MASTER OF SCIENCE

by

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A C K N O W L E D G E M E N T S

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ABSTRACT

The photochemistry of organometallic compounds is receiving increasing attention in the current literature, but as yet, little work has been reported on the photochemistry of metal-containing ketones.

The objective of the work reported in this thesis was the synthesis of ligands for the formation of suitable metal-containing ketones. The initial studies were directed at the preparation of β- and γ-hydroxyketones by a variety of methods, but the major effort was later concentrated on the synthesis of phosphorus derivatives of o-hydroxyphenyl alkyl ketones.

The reaction of o-hydroxyphenyl alkyl ketones with phosphorus trichloride afforded 2-chloro-1,3,2-dioxaphosphorinans which were readily converted to the corresponding 2-alkoxy derivatives by reaction with various alcohols. Extension of the study to acteylacetone indicated that an analogous reaction occurs to give highly labile products. This part of the work has been accepted for publication in *Chemical Communications*.

The reaction of o-hydroxyphenyl alkyl ketones with other phosphorus halides, such as dichloro phenylphosphine and chloro diphenylphosphine, has also been investigated. Reaction of the former reagent with o-hydroxyacetophenone gave a crystalline phosphorus-containing derivative; spectroscopic evidence indicates that this compound possesses an unusual structure and it is currently being studied by X-ray crystallography.

ABBREVIATIONS

The following abbreviations are used in the course of this thesis:

i.r.	infra-red
n.m.r.	nuclear magnetic resonance
g.l.c.	gas-liquid chromatography
t.l.c.	thin layer chromatography
THF	tetrahydrofuran
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
ether	diethyl ether
pet. ether	petroleum ether
mmol	millimole
b.p.	boiling point
m.p.	melting point
r.t.	room temperature
ν	infra-red stretching mode

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CHAPTER 1

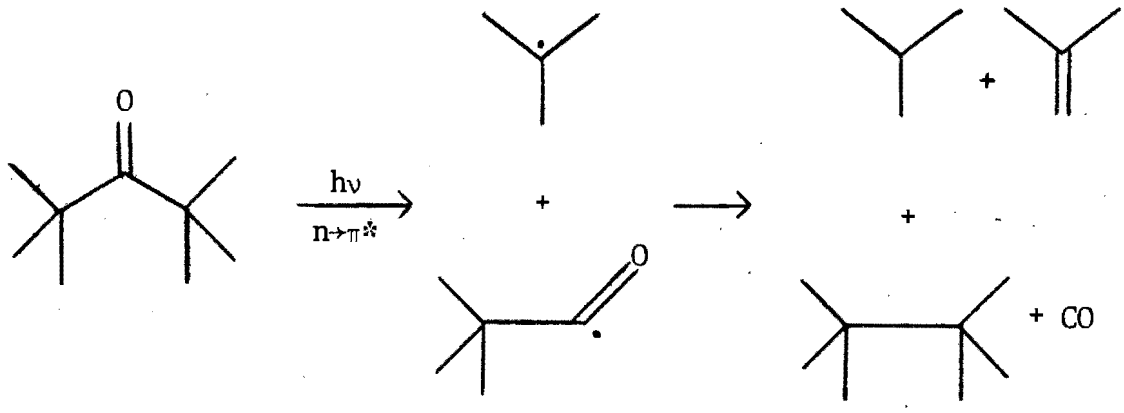
INTRODUCTION

CHAPTER 1

INTRODUCTION

The photochemistry of organic compounds and in particular ketones, has made considerable advances over the last decade. In the case of ketones, photochemical excitation is accompanied by chemical degradation. Two principal pathways are followed in the photolysis of ketones. The first involves α-bond cleavage[1], and is referred to as the Norrish type I process, an example of which is outlined in Scheme 1 below.

SCHEME 1



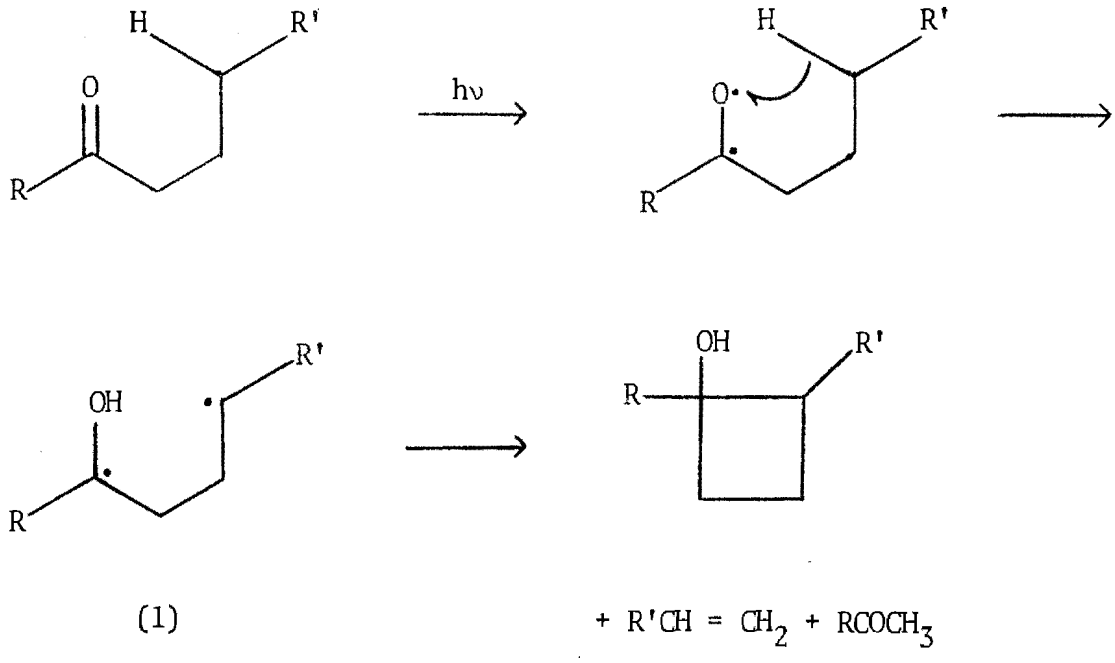
The n→π* excitation in ketones can be achieved by light of wavelength well above 200 nm.

Carbonyl compounds containing γ-C-H bonds undergo 1,5-hydrogen transfer to yield both cleavage and cyclisation products.[2,3] This cleavage reaction is called the Norrish type II process and is almost always followed by some cyclobutanol formation.

Because 1,5-hydrogen transfer yielded both cyclisation and elimination products, Yang[4] proposed that the reaction occurs via a 1,4 biradical such as (1) as a common intermediate. There is now little

doubt that ketones excited to the triplet state (hereafter referred to as ketone triplets) undergo type II processes exclusively via 1,4 biradicals (Scheme 2).

SCHEME 2



(1) + R'CH = CH_2 + $RCOCH_3$

[R = alkyl or aryl
R' = alkyl or H]

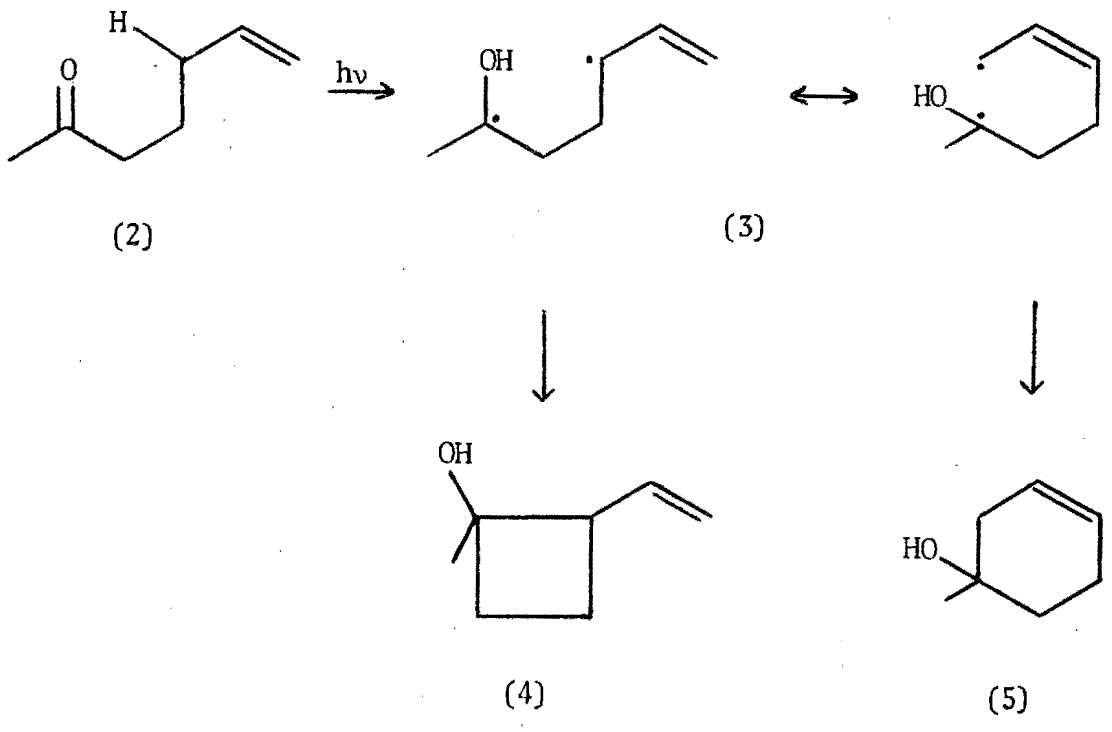
The proportion of various products formed depends on the reaction conditions and the nature of the groups R and R'. In most cases, however, cyclisation is a minor pathway.

Different facets of the type II process have been studied for butyrophenones, ring-substituted butyrophenones, valerophenones and ring-substituted valerophenones. The nature of the reactive state has been established[5] and for aromatic ketones both reactions occur only from the triplet state. Evidence for this fact is that the Norrish type II reaction of butyrophenone and valerophenone has been

shown to be quenched by piperylene and naphthalene which are known to be efficient triplet quenchers[6]. The effect of solvent polarity on quantum yield[7,8], as well as the effect of ring substituents[9] on the chemical reactivity of the ketone triplets has been studied. Polar solvents appreciably enhance the quantum efficiency with which aliphatic and aromatic ketones undergo photoelimination in solution. Quenching studies on valerophenone indicate that the life-time of the excited triplet state of the ketone does not vary more than a factor of four over a range of solvents. Consequently, it is inferred that the observed solvent effects arise from solvation of an hydroxy biradical intermediate rather than from any interaction with the excited state. The determination of the effects of ring substituents on the photochemistry of phenyl ketones is very complex. Phenyl, methoxy, methyl, o-chloro and p-chloro substituents decrease the chemical reactivity of the ketone triplets; trifluoromethyl substituents double reactivity; fluoro and m-chloro substituents produce little change and p-hydroxy, p-bromo and p-thiomethoxy substituents completely supress type II reaction. Aliphatic ketones, however, apparently undergo the reaction from both singlet and triplet excited states[2].

Yang *et al.* undertook the irradiation of hept-6-en-2-one (2) in order to provide direct evidence as to the mechanism of cyclobutanol formation[10]. If the reaction proceeds by a concerted mechanism, the only cyclic products formed would be cyclobutanols. If the intermediate is, however, a free radical, in this case an allyl radical (3), it may cyclise in two possible ways to form methylvinylcyclobutanols (4) as well as the methyl cyclohexenol (5) as shown in Scheme 3.

SCHEME 3

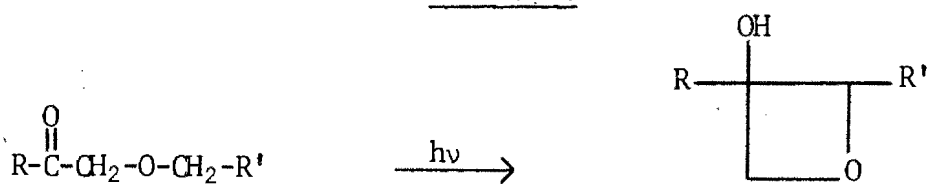


(2) (3) (4) (5)

The isolation of both (4) and (5) conclusively substantiates the step-wise mechanism.

The synthetic utility of the Norrish type II process continues to be exploited. It has been found that a cognate reaction can be effected with α-alkoxyketones (6), providing a method for the preparation of 3-oxetanols (7)[11] as shown in Scheme 4.

SCHEME 4

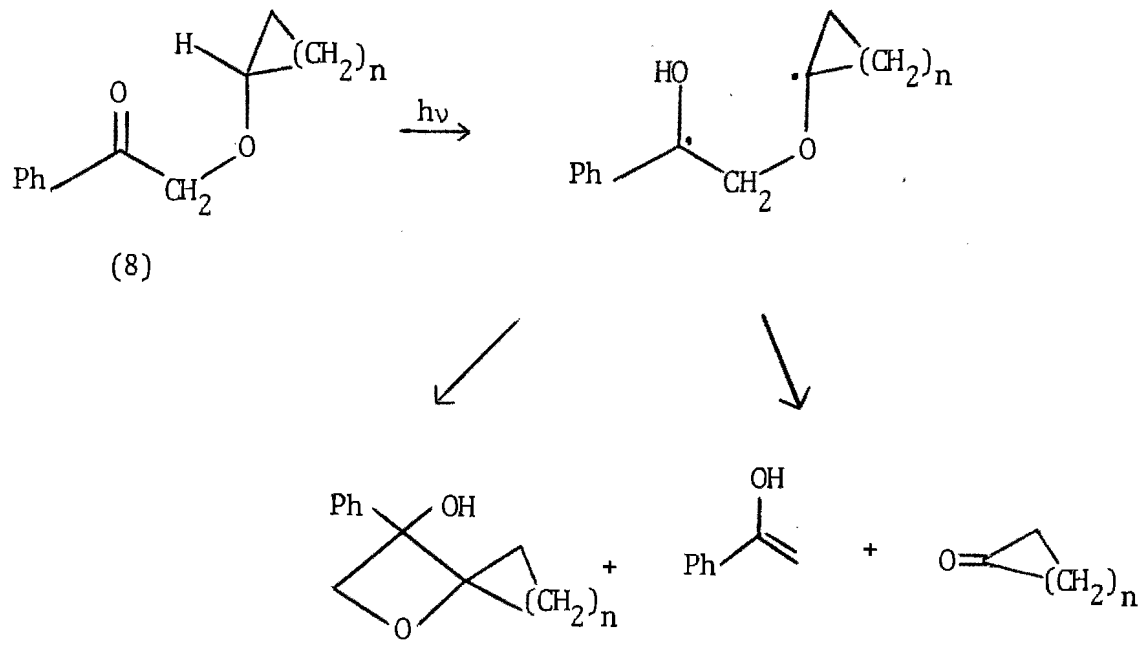


(6) (7)

R =	C_6H_5	;	R' =	H	:	29%
R =	C_6H_5	;	R' =	CH_3	:	34%

On excitation α-cycloalkoxyacetophenones (8) give cyclisation and elimination products resulting from the intermediate 1,4 biradical[12]. Cyclisation gives rise to oxaspirans (9) (Scheme 5).

SCHEME 5

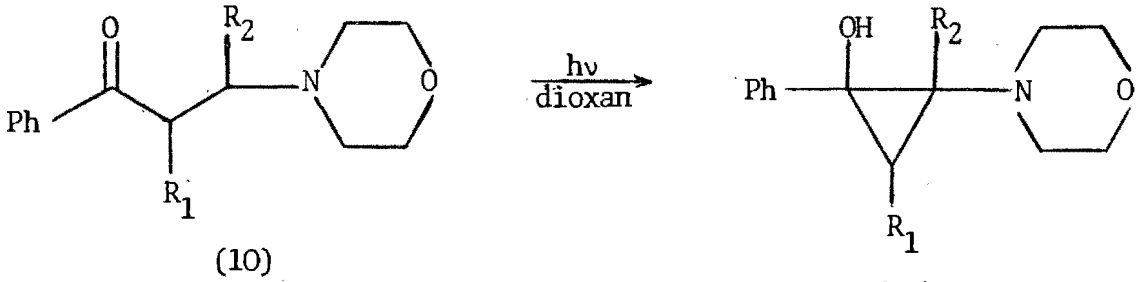


(8) (9)

[n = 1-5, 35-78%]

Photolysis of morphilinoketones (10) affords aminocyclopropanols (11) in good yield[13]. In this case β-hydrogen abstraction occurs. The formation of three-membered rings is a novelty (Scheme 6).

SCHEME 6

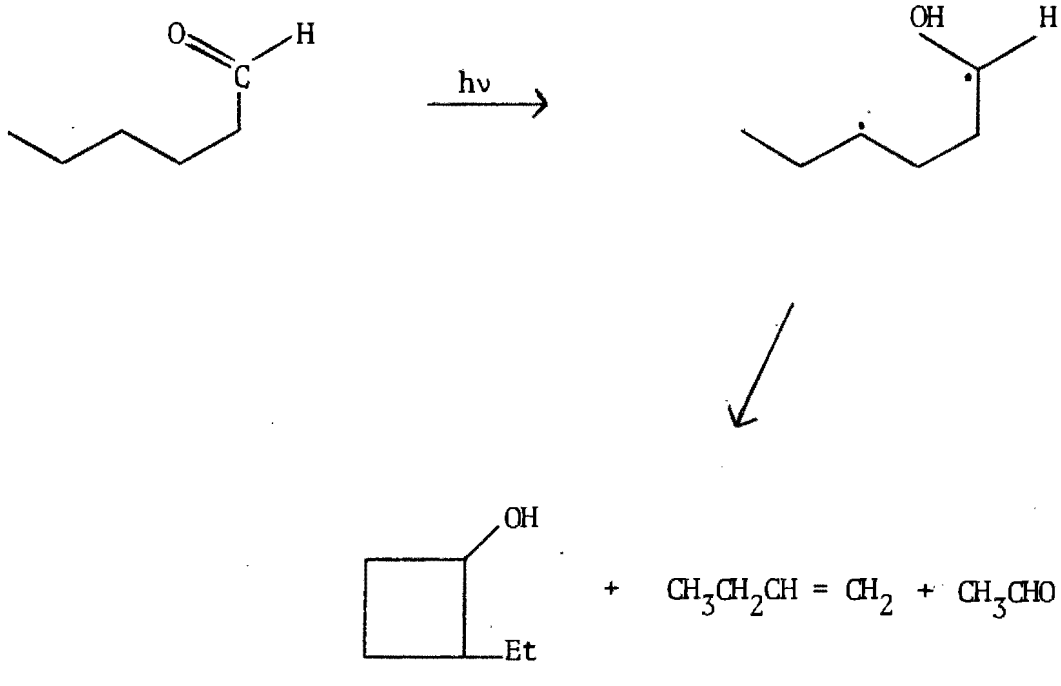


(10) (11)

R_1	=	Me		R_2	=	H	80%
R_1	=	Ph		R_2	=	H	95%
R_1	=	H		R_2	=	Ph	85%

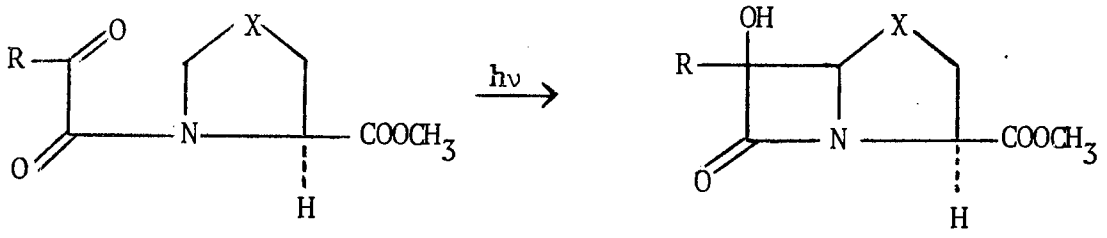
Aldehydes also undergo the Norrish type II process an example of which is given in Scheme 7[14].

SCHEME 7



The Norrish type II photoreaction has also been used in an approach to the synthesis of penicillin derivatives[15]. The compounds (12; R = CH_3) were cyclised in variable yields in benzene solution to the bicyclic compounds (13); the aldehyde [(12); R = H, X = SO] was also cyclised successfully (Scheme 8).

SCHEME 8

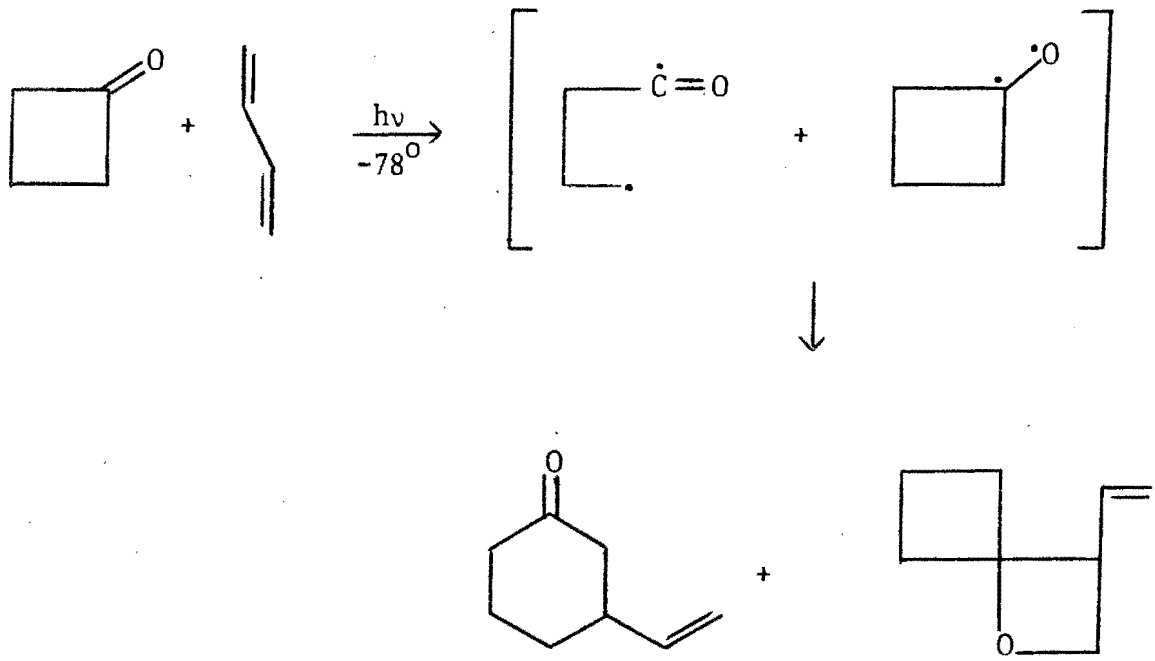


(12) (13)

R = CH_3;	X = S	11%	
	SO	8% isolated, 40% as estimated by spectroscopy	
	SO_2	70%	

Although the evidence for the intermediacy of 1,4 biradicals in triplet state type II photoelimination processes is compelling[16], no successful attempt to trap such a biradical has yet been reported, despite the fact that conjugated dienes apparently trap the 1,4 biradicals produced by photolysis of cyclobutanones[17] (Scheme 9). The oxetane (14) is also formed under these conditions.

SCHEME 9

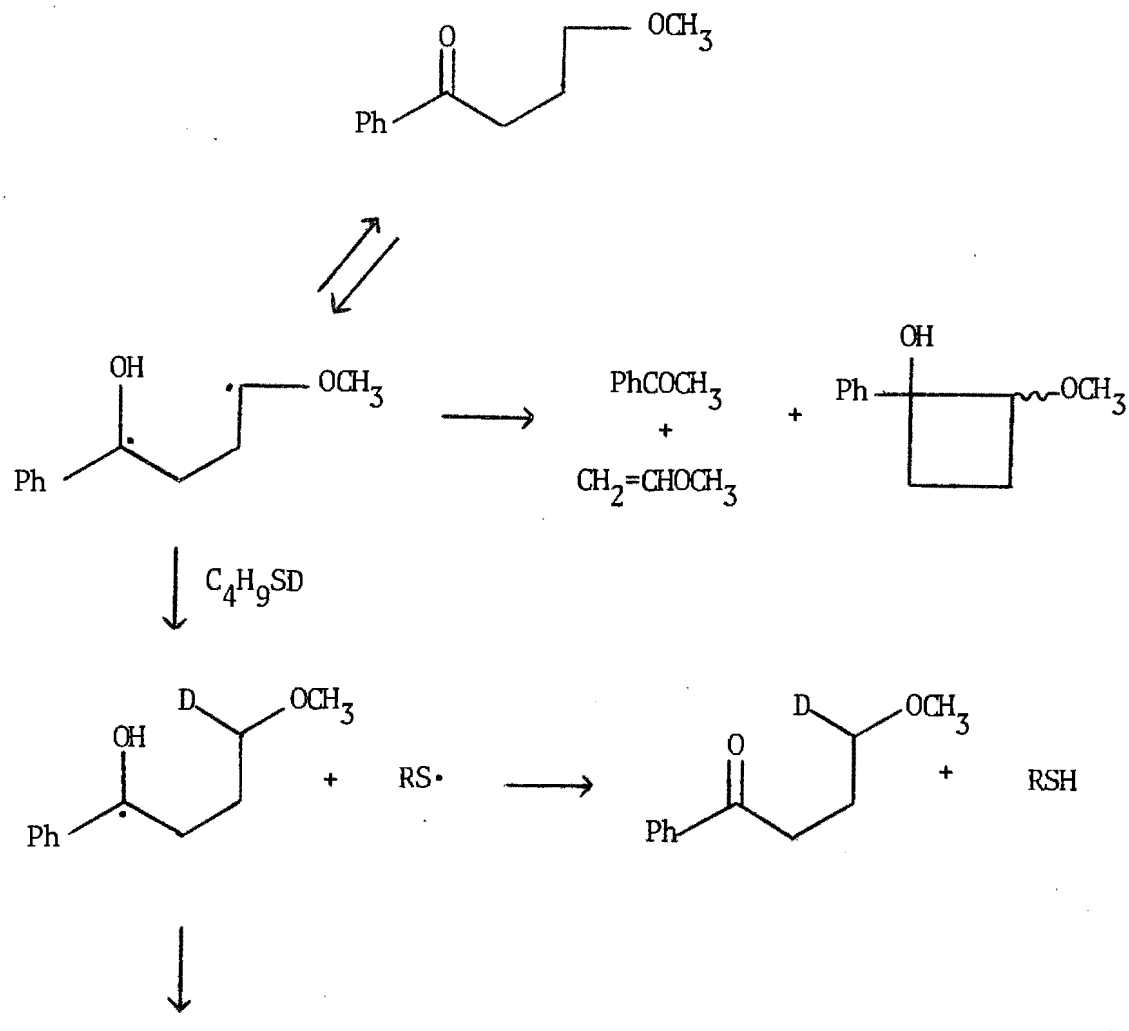


(32%) (14)

(32%)

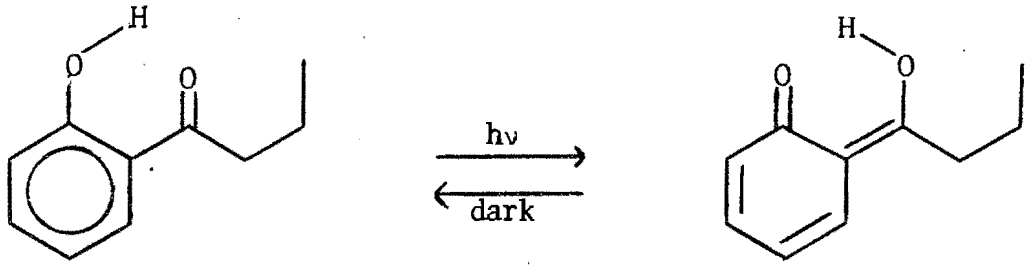
Wagner and Zepp[18] have found that alkyl mercaptans are able to trap very efficiently the biradicals produced from phenyl alkyl ketones. Their evidence is based on kinetics and labelling experiments. A possible pathway is outlined in Scheme 10 which summarises what appears to happen.

SCHEME 10



It has been reported[19] that hydroxyarylalkyl ketones of the type (15) shown below, undergo reversible photoenolisation and not the Norrish type II photoelimination process (Scheme 11).

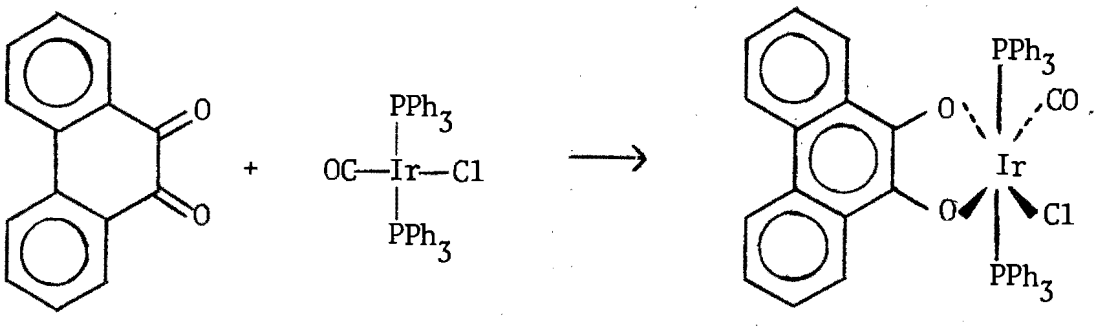
SCHEME 11



(15)

There have been no reports, however, of transition metal compounds being employed in the photochemistry of ketones. Such compounds have, however, been employed in organic photochemistry; for example, the photoinduced oxidative addition of 9,10 phenanthrene-quinone (16) to $[Ir(PPh_3)_2(CO)(Cl)]$ (17) has been reported[20], (Scheme 12). The metal complex (17) apparently serves to trap electronically excited states of o-quinones.

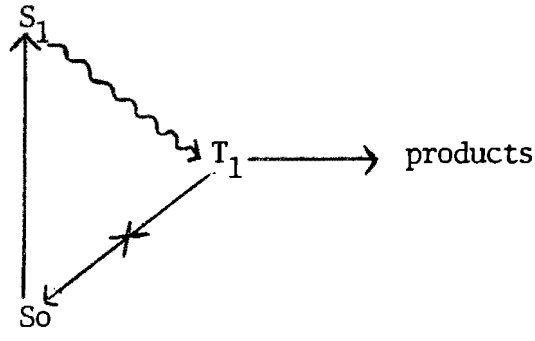
SCHEME 12



(16) (17)

Scheme 13 outlines the modes of deactivation open to excited states[21].

SCHEME 13



So ground state singlet

S_1 excited state singlet

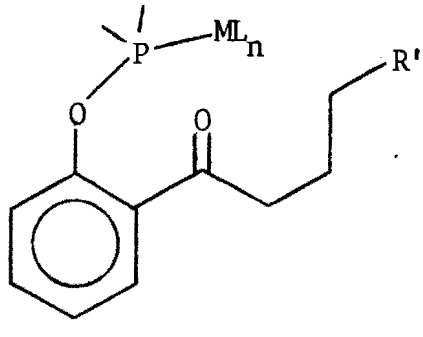
T_1 excited state triplet

⇝ denotes intersystem crossing

Since ground state to triplet state transitions are forbidden, intersystem crossing is the main source of excited triplets. T_1 is a relatively long-lived species and can therefore decompose to products. It has been reported[22] that the presence of heavy atoms, unpaired electrons or a magnetic field results in a breakdown of the selection rules, and triplet to singlet conversions then take place, even though according to the rules of spin conservation they are not allowed (Scheme 13). It must be noted that because the triplet to singlet transition can occur more easily in the presence of a heavy atom the type II process might be quenched. An example[23] of the "intermolecular heavy atom effect" is provided by the absorption spectrum of 1-chloronaphthalene measured as the pure liquid and in ethyl iodide solution. Although both of these substances are individually colourless, their binary solution is yellow. This is due to an enhancement of spin-orbit coupling induced by ethyl iodide in the halonaphthalene, which causes sufficient enhancement of the usually unmeasurable

So + hν → T_1 transition to produce a yellow colour.

It is anticipated that the addition of transition metal complexes to photochemical reactions of organic compounds might alter completely the reaction pathway of the excited species. Furthermore, the metal could impart selectivity to the degradation thereby enhancing its synthetic applications. Another important aspect is that the addition of transition metal ions could lead to a trapping of the biradical intermediate (1) to yield stable organometallic compounds. Excited species are, however, generally very short-lived and, under the dilutions used in photochemistry, the probability of intermolecular interaction between the biradical species and the metal derivative would be extremely small. This difficulty could be overcome by prior co-ordination of the metal to the organic species being irradiated as illustrated by structure (18)

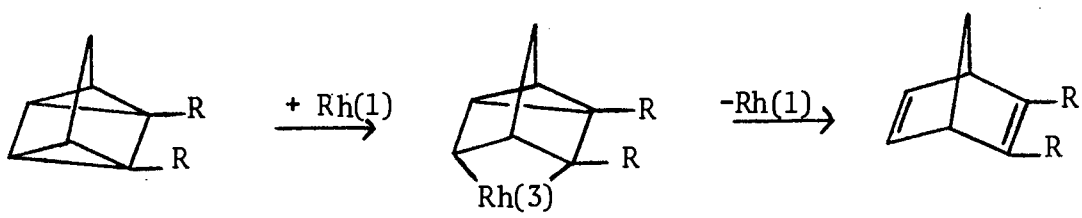


(18)

Because the metal in such compounds would be held close to the biradical formed during photolysis, there is a possibility that the biradical may be trapped, even though the T_1 → So transition (leading to quenching) would be facilitated by its presence.

The aim of this study is to synthesise and observe the photochemistry of metal containing ketones in order to determine the influence of the metal on the photolysis of ketones as well as attempting to trap the biradical intermediate (1). Rh(1) and Fe(0) were the metals chosen for this study in view of their property to insert into carbon-carbon bonds and their capacity to undergo oxidative addition; for example Rh(1) is easily converted to Rh(3)[24] (Scheme 14).

SCHEME 14



[R = $COOCH_3$, CN]

The second order rate constants of the isomerisation of the quadricyclanes in $CDCl_3$ were determined by following the conversion with N.M.R. spectroscopy using [Rh_2(norbornadiene)$_2Cl_2$] as a catalyst.

The ketones chosen for the study were of the type $RCOCH_2CH_2OH$ and $RCOCH_2CH_2CH_2OH$ where R is an alkyl group such as n-propyl or n-butyl, as well as aromatic ketones such as orthohydroxybutyrophenone and orthohydroxyvalerophenone. As the aim was to trap the biradical intermediate, there should be little or no interaction between the keto-group and the metal. As Rh(1) is a 'soft' metal[25], a 'soft' ligand is required to form a strong metal-ligand bond and thus a stable complex. Phosphorus was chosen,

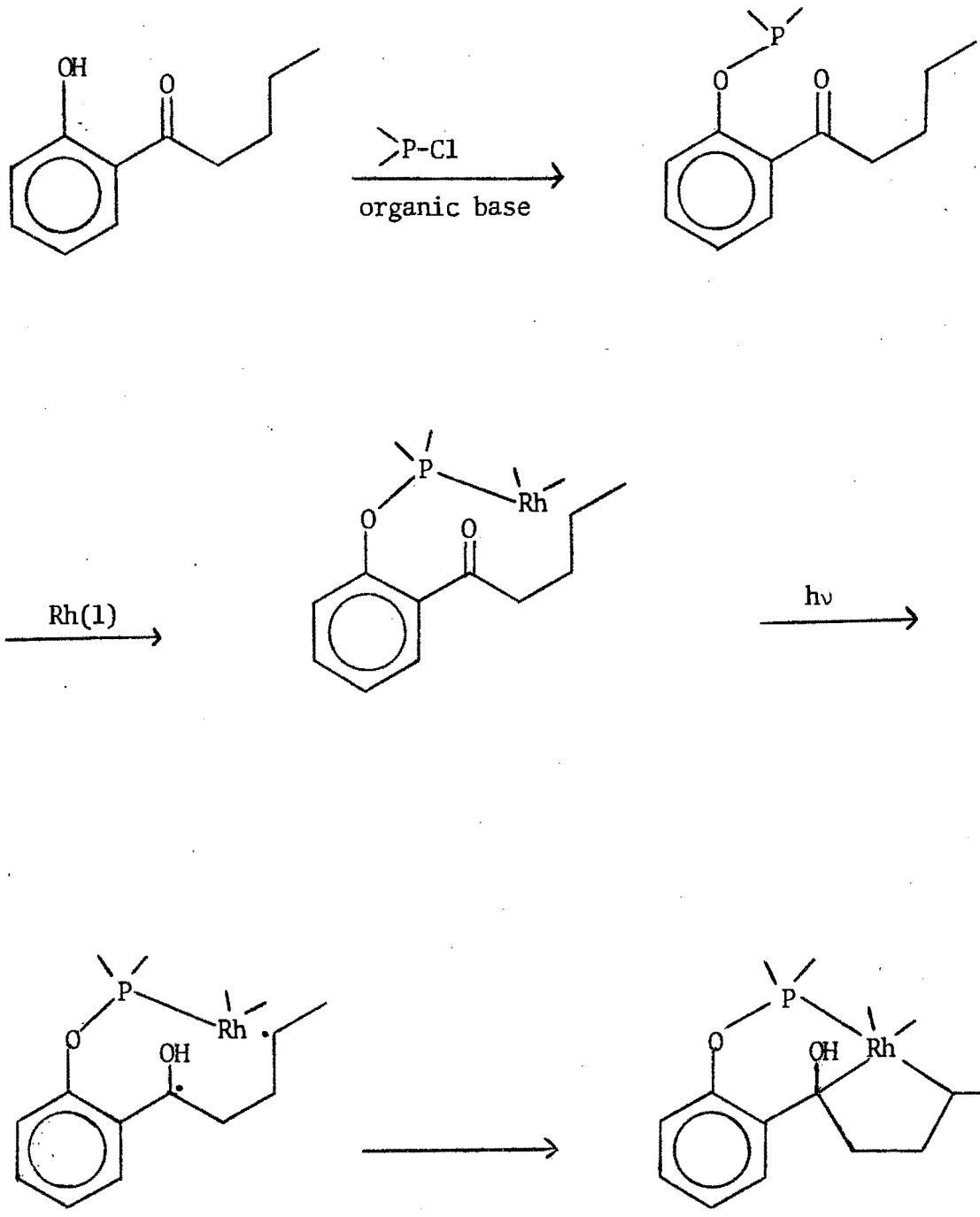
therefore, to act as a bridge between the metal and the ketone. A method which lends itself readily to the formation of phosphorus ligands is the reaction of phosphorus halides[26,27,28] with hydroxyl groups to give compounds of the type $>$P-OR. In this respect, it must be noted that the formation of an aryloxyphosphorus derivative from o-hydroxybutyrophenone or o-hydroxyvalerophenone, as opposed to the formation of an alkoxyphosphorus derivative from an aliphatic hydroxyketone, has the advantage that the former are less susceptible to rearrangement. This is illustrated by the Michaelis-Arbuzov rearrangement[29] (Scheme 15) which occurs far more readily when R is an alkyl as opposed to an aryl group.

SCHEME 15

$$P(OR)_3 + R'X \rightarrow [(RO)_3PR'X] \rightarrow O=P(OR)_2R' + RX$$

A schematic representation of the proposed investigation is given below using an aromatic ketone as an example (Scheme 16).

SCHEME 16



CHAPTER 2

THE SYNTHESIS OF HYDROXY KETONES

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The photochemical studies described in Schemes 2 and 16 (Chapter 1) require the prior synthesis of β- and γ-hydroxy ketones of the type $RCOCH_2CH_2OH$, $RCOCH_2CH_2CH_2OH$ and o-HOC_6H_4COR (R = Pr^n or Bu^n). Initial studies were directed at the synthesis of acyclic hydroxy-ketones (Sections 2.1 and 2.2), but in view of difficulties encountered, later efforts were directed mainly at the synthesis of the derivatives of the more readily accessible o-hydroxyphenyl alkyl ketones (Section 2.4 and Chapter 3).

The Synthesis of Acyclic Hydroxy Ketones.

2.1 γ-Hydroxy Ketones

The first synthetic approach attempted is outlined in Scheme 17.

SCHEME 17

$$CH_2{=}CHCH_2Br \xrightarrow{Mg,\ ether} CH_2{=}CHCH_2MgBr \xrightarrow[2)\ H_3O^{\oplus}]{1)\ RCHO\ in\ ether}$$

$$RCH(OH)CH_2CH{=}CH_2 \xrightarrow{oxidation} RCOCH_2CH{=}CH_2 \xrightarrow[p\text{-}TsH,\ PhH,\ \Delta]{HOCH_2CH_2OH}$$

(19) (20)

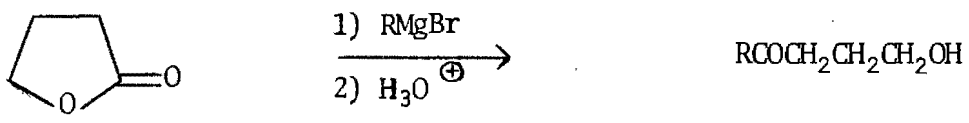
$$\underset{\text{RCCH}_2\text{CH=CH}_2}{\overset{\ulcorner\urcorner}{\text{O O}}} \xrightarrow[2)\ H_2O_2/OH^{\ominus}]{1)\ 9\text{-BBN, THF, }\Delta} \underset{\text{RCCH}_2\text{CH}_2\text{CH}_2\text{OH}}{\overset{\ulcorner\urcorner}{\text{O O}}} \xrightarrow{H_3O^{\oplus}} RCOCH_2CH_2CH_2OH$$

[R = Pr^n or Bu^n ; 9-BBN = 9-Borabicyclo [3.3.1] nonane]

The Grignard reaction leading to the formation of 1-hepten-4-ol (19; R = Pr^n) proceeded smoothly and in good yield. In the oxidation of the unsaturated alcohol care had to be exercised to avoid isomerisation of the β,γ- to the α,β-unsaturated system. Oxidation according to the method of Brown[30], using the two phase system of chromic acid and an ether solution of the alcohol, gave mixtures of the desired ketone and starting alcohol under a variety of conditions. Thus mixtures were obtained even when a large excess of chromic acid was used. Attempted separation of the alcohol and ketone by fractional distillation led to isomerisation of the ketone to the α,β-unsaturated system on the basis of i.r. and n.m.r. spectra of the products. Care was taken to remove any traces of acid prior to distillation. Oxidation using chromium trioxide and 3,5-dimethylpyrazole, a method developed by Corey[31] and reported to proceed in excellent yields, likewise gave mixtures of the ketone and starting alcohol in low yield. In view of the difficulties encountered in the oxidation of the unsaturated alcohol and the separation of the product ketone from the starting material, the approach outlined in Scheme 17 was discontinued.

An alternative approach to the synthesis of the γ-hydroxy ketone is outlined in Scheme 18.

SCHEME 18

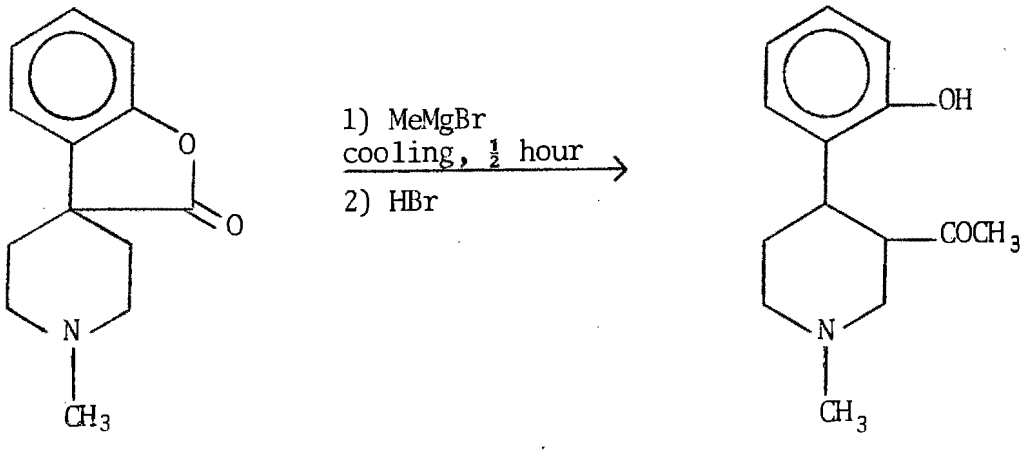


[R = Bu^n]

It was reasoned that, if excess γ-butyrolactone was used in the reaction

with the Grignard reagent, the possibility of forming a tertiary alcohol by further reaction of the ketone product would be minimised. In this respect the formation of a ketone from the lactone (21) has been reported to proceed in high yield (Scheme 19)[32].

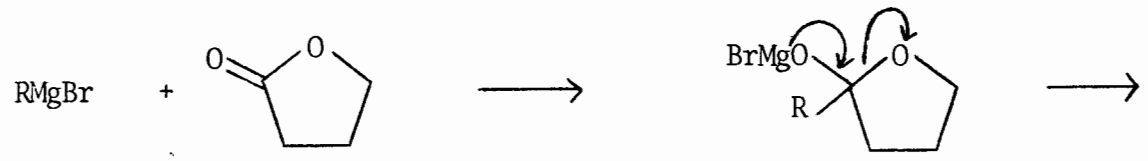
SCHEME 19

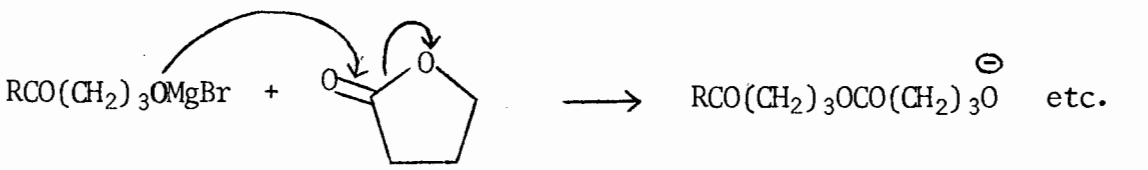


(21) 82%

Addition of preformed n-butyl magnesium bromide to excess γ-butyrolactone at 0°C resulted in the formation of a mixture containing some hydroxyketone as indicated by the i.r. spectrum of the products. Repetition of the reaction at room temperature gave a product mixture whose i.r. spectrum indicated the presence of unchanged lactone, ketone and an ester, thought to be formed as shown in Scheme 20.

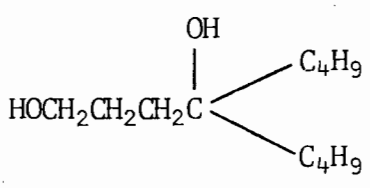
SCHEME 20





[R = Bu^n]

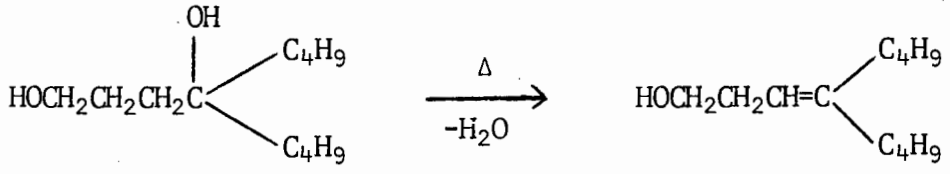
Use of equimolar amounts of Grignard reagent and γ-butyrolactone gave a product mixture shown by g.l.c. to consist of at least five components, none of which corresponded to the starting lactone. Use of a slight molar excess of Grignard reagent gave a mixture consisting of seven components. Attempted separation of the components by column chromatography failed. Repetition of the reaction using equimolar amounts of the reagents on a large scale, followed by fractional distillation of the product, gave the diol (22) in 20% yield.



(22)

This diol was also isolated from a large scale preparation carried out

at -45°. Distillation of the crude alcohol gave a less viscous product having a shorter retention time than the starting alcohol on g.l.c. analysis. The same product was formed on heating the alcohol under reflux in chloroform both in the absence or presence of an acid catalyst. ^{1}H n.m.r. and i.r. spectral analysis of the product indicated that it was an alkenol of the type (23), formed by dehydration of the tertiary alcohol (22).

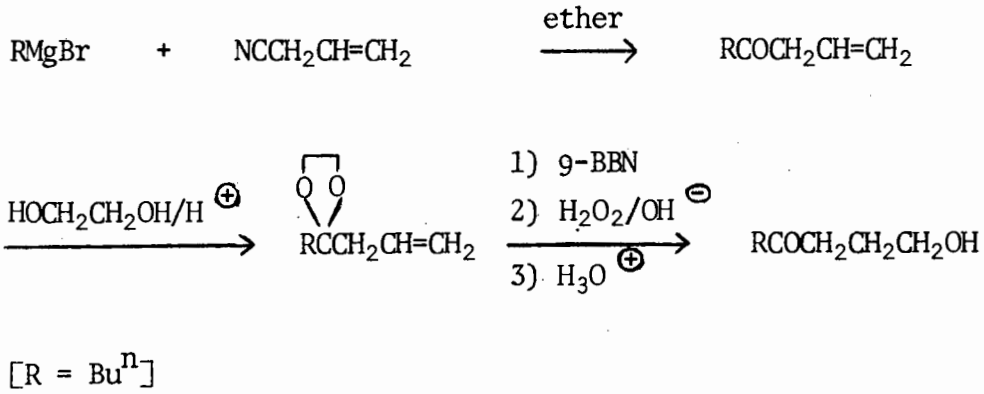


(22) (23)

The above results indicated that the approach envisaged in Scheme 18 would not provide a satisfactory route to the γ-hydroxyketones.

The reaction of nitriles with Grignard reagents, followed by acid hydrolysis, is quoted in many modern texts as being a convenient method for the efficient synthesis of ketones[33]. It was decided to apply this reaction to the synthesis of γ-hydroxyketones as outlined in Scheme 21.

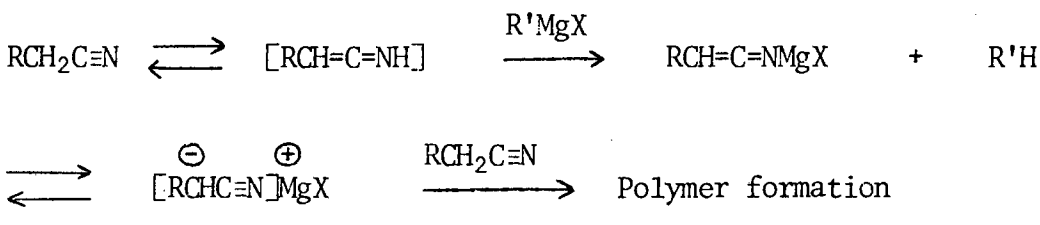
SCHEME 21



[R = Bu^n]

Reaction of the allyl nitrile with n-butyl magnesium bromide, however, resulted in the formation of polymeric material with no ketone absorption being observed in the i.r. spectrum of the product. In order to establish the optimum reaction conditions, acetonitrile and n-butyl magnesium bromide were reacted to give 2-hexanone. The yield of ketone was extremely low and a large amount of polymeric material was formed during the reaction. An investigation of the literature revealed that acetonitrile and phenylacetonitrile give practically none of the desired ketone by this method[34], probably because of a tendency of these nitriles to react in the imino form as illustrated in Scheme 22.

SCHEME 22



[R = H or Ph]

The failure of the reaction with allyl nitrile can also be attributed to the activated nature of the methylene group. Higher homologues of acetonitrile and aromatic nitriles, however, are reported to give good yields of ketone by this method[34].

2.2 β-Hydroxy Ketones

It was then decided to attempt the synthesis of β-hydroxy ketones as outlined in Scheme 23.

SCHEME 23

$$CNCH_2CH_2OH + 2RMgBr \xrightarrow{\text{ether}} RCCH_2CH_2OMgBr \quad (NMgBr)$$

$$\xrightarrow{H_3O^{\oplus}} RCOCH_2CH_2OH$$

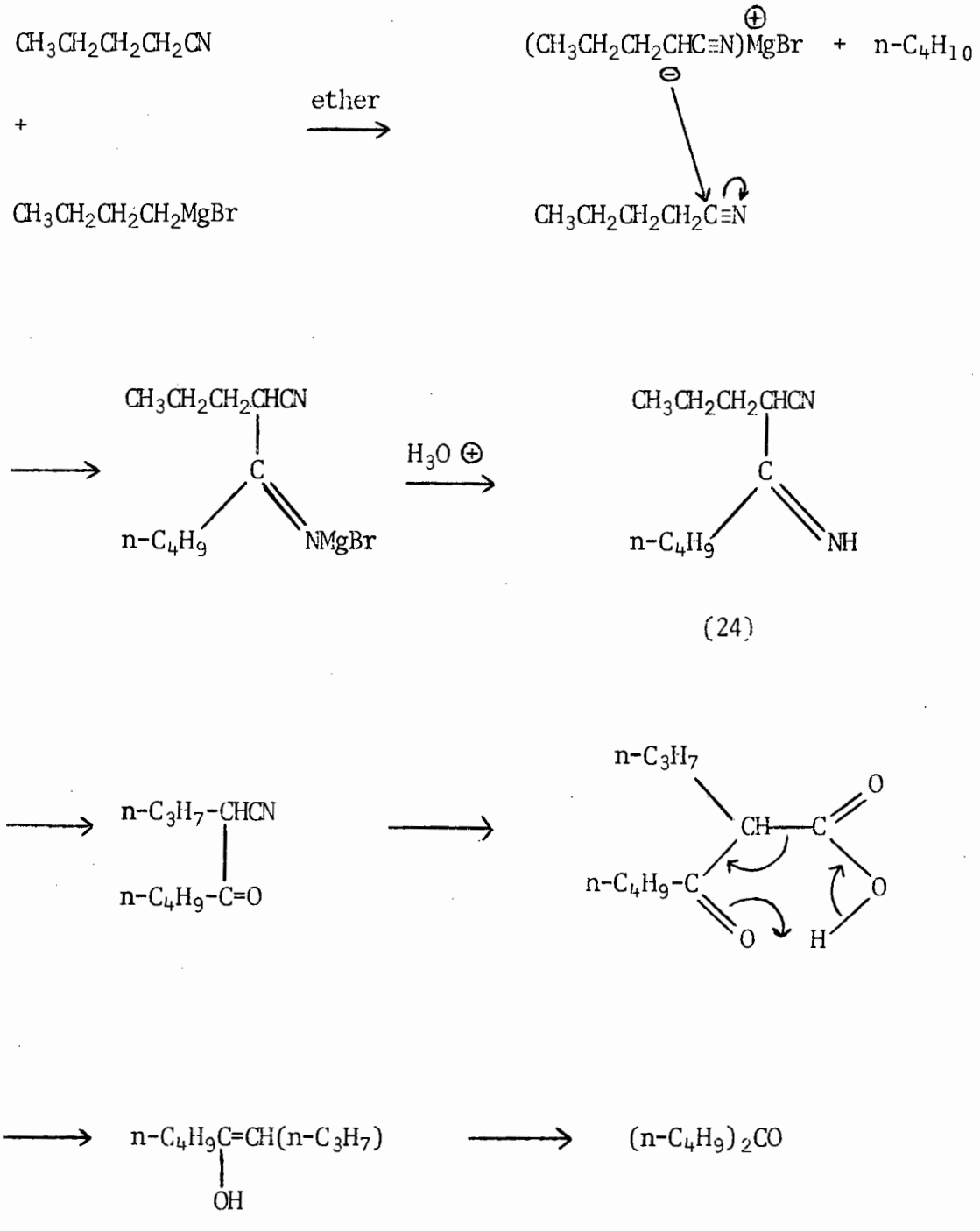
[R = Pr^n, Bu^n]

In order to optimise reaction conditions the synthesis of 5-nonanone via reaction of n-butyl magnesium bromide with pentanenitrile was investigated.

$$n\text{-}C_4H_9CN \xrightarrow[2)\ H_3O^{\oplus}]{1)\ n\text{-}C_4H_9MgBr} (n\text{-}C_4H_9)_2CO$$

The i.r. spectrum of the product obtained when using diethyl ether as solvent in the Grignard reaction indicated the presence of ketone, nitrile and imine [ν(C=O) 1710; ν(C≡N) 2195; ν(NH) 3385; ν(C=N) 1640 cm^{-1}], while in tetrahydrofuran, only nitrile and imine were detected in the product. Treatment of the products by heating them under reflux in aqueous tetrahydrofuran or with sulphuric acid in ether at room temperature resulted in partial conversion of the imine to the ketone. Repetition of the reaction using a 20% excess of Grignard reagent gave similar results and t.l.c. of the product indicated that very little unreacted starting nitrile was present. Vacuum distillation of the product obtained from a second reaction in tetrahydrofuran gave a pale yellow liquid which analysed for $C_{10}H_{18}N_2$ (M^+, m/e 166); its i.r. spectrum indicated the presence of both nitrile and imine groups, with an exchangeable proton being detected by ^1H n.m.r. The formation of the α-cyano-imine (24) may occur as shown in Scheme 24.

SCHEME 24

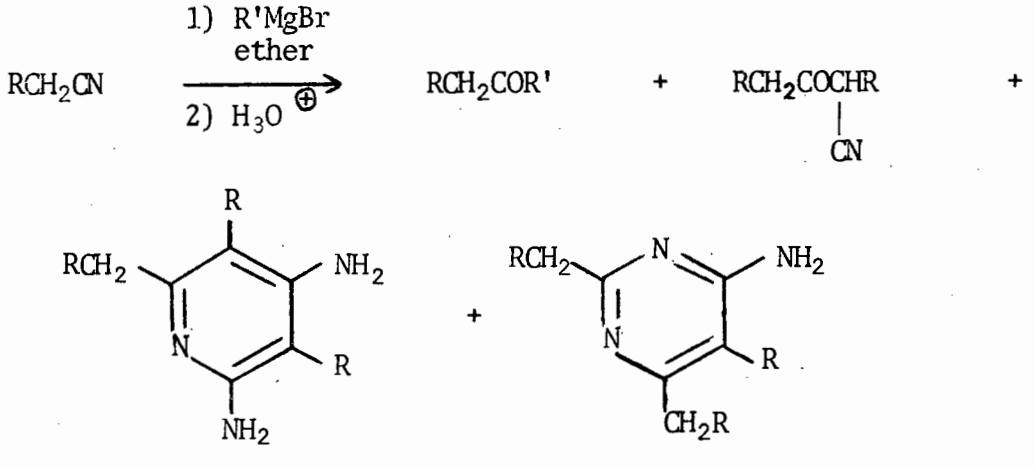


Thus the formation of the α-cyano-imine (24) (and the polymeric materials) proceeds via abstraction of an α-hydrogen from the nitrile, followed by condensation with unchanged nitrile. The

α-cyano-imine may be further hydrolysed to the α-cyano-ketone and, on prolonged acid treatment, this is converted to the ketone presumably via decarboxylation of the β-keto-acid (Scheme 24).

A survey of the literature revealed that the condensation of nitriles containing α-hydrogens in the presence of Grignard reagents was reported by Bruylants as early as 1921[35], and it is briefly mentioned by Kharasch and Reinmuth[36]. Hauser and Humphlett carried out a detailed investigation of the effect of the structure of the nitriles and Grignard reagents on the course of the reaction, and observed that the extent of condensation leading to the α-cyano-imine and polymers was strongly dependent on the degree of activation of the α-hydrogens of the nitrile and the nature of the Grignard reagent[37]. Some of the products formed in the reaction of nitriles with Grignard reagents are shown in Scheme 25.

SCHEME 25

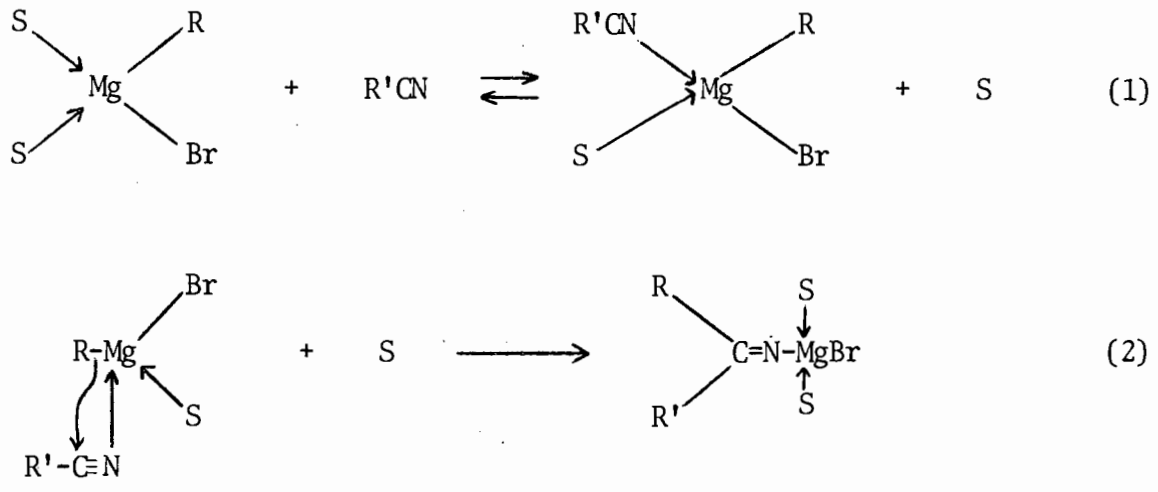


In general, the yields of the desired ketone obtained in reactions with phenyl (and aryl) Grignard reagents are considerably higher than those obtained with alkyl Grignard reagents, indicating a greater tendency towards α-hydrogen abstraction with the latter

reagents. In addition, it was found that use of sterically hindered Grignard reagents, such as t-butylmagnesium chloride, resulted in an even lower yield of ketone[37]. Nitriles containing activated α-hydrogens, such as phenylacetonitrile and acetonitrile, react to give mainly condensation products. Increased yields of ketone may, however, be obtained by use of a large excess (300%) of the Grignard reagent[38]. The reaction of allyl nitrile with Grignard reagents (Scheme 21) may thus also be presumed to proceed with predominant formation of condensation products.

In the above studies exclusive use was made of ethers as solvents. Recently Kirrman and Rabesiaka have studied the influence of the solvent on the reaction, and have shown that the solvent plays a critical role in determining the nature of the product formed[39]. They concluded that use of a weakly basic solvent, such as N,N-diethylaniline, generally gives superior yields of the ketone (> 70%; determined by g.l.c. analysis) to those obtained using more basic solvents, such as triethylamine. They have proposed that the solvent participates in the reaction as shown in Scheme 26.

SCHEME 26



The displacement of strongly basic solvents by the nitrile as in step (1) is difficult, and the abstraction of the α-hydrogen of the nitrile predominates. In contrast, weakly basic solvents as N,N-diethylaniline, are more easily displaced, thus permitting the addition reaction of the Grignard reagent to the nitrile to be favoured, as in step (2).

The synthesis of 4-octanone using N,N-diethylaniline as a solvent according to the procedure of Kirrman and Rabesiaka and as shown in Scheme 27 was undertaken in order to establish the optimum conditions for the reaction.

SCHEME 27

$$n\text{-}C_4H_9CN \xrightarrow[2)\ \text{dilute } H_2SO_4]{1)\ n\text{-}C_3H_7MgBr,\ PhNEt_2} C_4H_9COC_3H_7$$

Addition of the nitrile to the Grignard reagent in N,N-diethylaniline at 70°, followed by stirring for one hour at 70° and standing at room temperature overnight, gave a homogeneous solution which indicated that addition of the nitrile to the Grignard was the dominant reaction[39], (observation of a heterogeneous mixture indicates that

α-hydrogen abstraction has occurred[39]. The i.r. spectrum of the product obtained after acid hydrolysis indicated the presence of a ketone [ν(C=O) 1722 and 1715 cm^{-1}] and a small amount of unchanged nitrile [ν(C≡N) 2265 cm^{-1}], while g.l.c. analysis indicated that the mixture contained one major as well as several minor components. Distillation led to the isolation of 4-octanone (25%), as well as a small amount of α-cyano-imine [ν(C≡N) 2195 cm^{-1}]. No 5-nonanone was isolated, indicating that the reaction proceeded mainly by addition to the nitrile with little α-hydrogen abstraction occurring (see Scheme 24).

Although the yield of 4-octanone reported above was somewhat lower than expected it was decided to attempt the synthesis of 1-hydroxy-3-hexanone according to the method proposed in Scheme 23 using N,N-diethylaniline as a solvent. 3-Hydroxypropanenitrile and n-propyl magnesium bromide in the molar ratio of 1:2 were reacted as above. G.l.c. analysis indicated the presence of a number of components in addition to polymeric material. In a subsequent reaction, the hydroxyl group was first protected as a tetrahydropyranyl ether; (this ether is stable to Grignard reagents[40]); however, hydrolysis of the addition product with either dilute sulphuric acid or saturated ammonium chloride solution yielded only polymeric material. It is possible that the β-hydroxyketone is unstable and dehydrates to give the corresponding α,β-unsaturated ketone, which, under the conditions of hydrolysis, polymerises.

2.3 The Synthesis of Ketones via the Addition of Grignard Reagents to Nitriles : An Evaluation of the Utility of the Reaction

The investigation of Hauser and Humphlett on the effect of the structures of the nitriles and Grignard reagents on the course of their

reaction[37], indicated that α-hydrogen abstraction, leading to α-cyano-imine and polymer formation, predominates in the reaction of primary alkyl nitriles and alkyl Grignard reagents in ether solvents. (Section 2.2). The studies of Kirrman and Rabesiaka on the influence of solvent on the course of the reaction indicated that these difficulties might be overcome by use of a weakly basic solvent, such as N,N-diethyl-aniline, but their results were based mainly on g.l.c. analysis of the products[39]. The synthesis of 4-octanone was thus investigated further in an attempt to establish the optimum conditions for the reaction. The product obtained by reacting equimolar amounts of n-propyl magnesium bromide with pentanenitrile under the conditions used by Kirrman and Rabesiaka was a mixture shown, by g.l.c. analysis, to contain 4-octanone, N,N-diethylaniline and small amounts of 1-bromopropane and 5-nonanone (formed by self-condensation of the nitrile). Fractional distillation of the mixture gave 4-octanone in 37% yield, much lower than the yields (70-95%) quoted by Kirrman and Rabesiaka for similar reactions. While the yields indicated by g.l.c. are high, the isolation of the ketone is undoubtedly complicated by the presence of the high boiling N,N-diethylaniline. The same reaction was repeated using ether as a solvent and, on hydrolysing the addition product with saturated ammonium chloride solution followed by very dilute hydrochloric acid, a mixture of products was obtained, the major component of which was 4-octanone. Fractional distillation yielded the ketone in 51% yield. This was a surprising result in the light of the observations by Kirrman and Rabesiaka that yields of ketone obtained from reactions carried out in ether were lower than when N,N-diethylaniline was used as a solvent; this result does, however, illustrate the danger of judging the efficiency

of a reaction purely on yields determined by g.l.c. rather than isolated yields of pure product. In the synthesis of 1-phenyl-1-pentanone (n-valerophenone) from pentanenitrile and phenyl magnesium bromide in ether a 71% yield was obtained, supporting the observations made by Hauser and Humphlett that the yield of the desired ketone obtained in reactions with aryl Grignard reagents is considerably higher than those obtained with alkyl Grignard reagents[37].

$$CH_3CH_2CH_2CH_2CN + PhMgBr \xrightarrow[2)\ NH_4Cl\ soln]{1)\ ether} CH_3CH_2CH_2CH_2COPh$$

71%

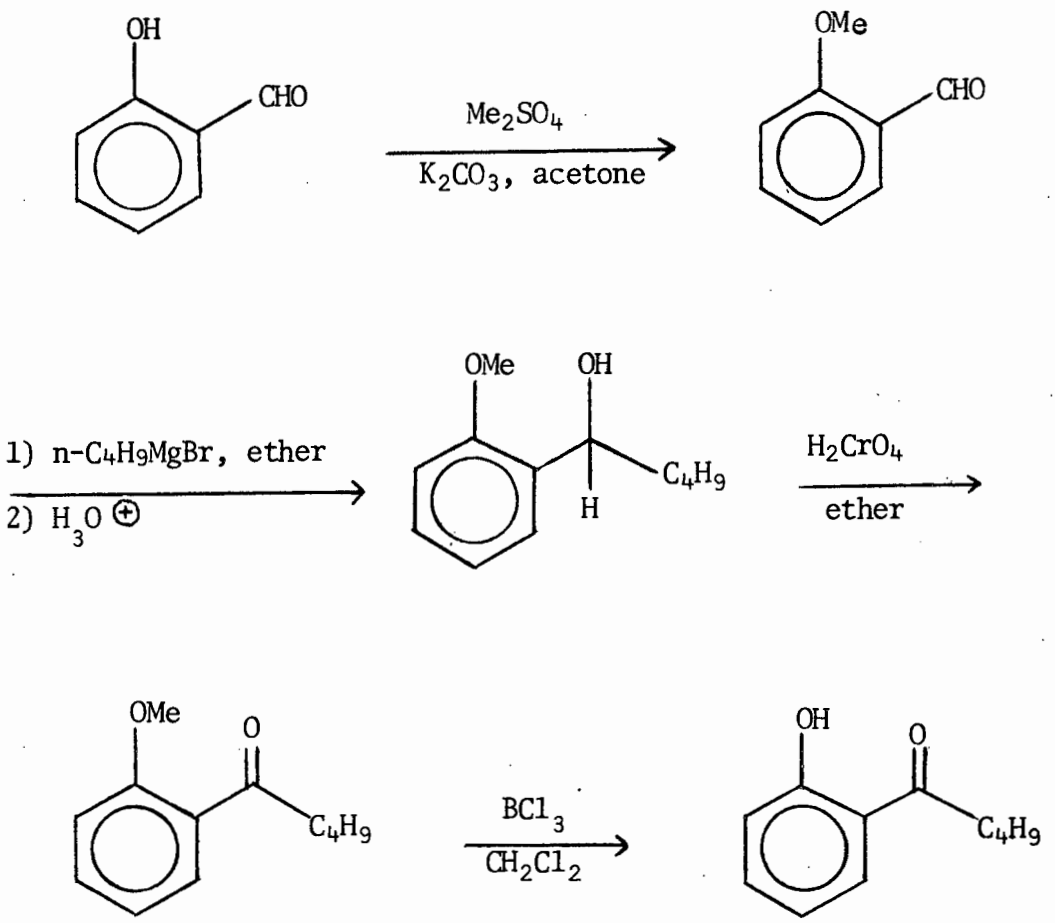
In summary, it may be stated that while Grignard reagents react with aryl nitriles to give, after hydrolysis, high yields of the corresponding ketones, the yields of ketones obtained in similar reactions with alkyl nitriles containing α-hydrogens are strongly dependent on the structures of the nitrile and Grignard reagent, and on the solvent used in the reactions. Aryl Grignard reagents generally give good yields of the ketones in ether, but alkyl Grignard reagents give considerable amounts of condensation products, formed via abstraction of an α-hydrogen from the nitrile. The yields of ketone relative to condensation products can be increased by use of a weakly basic solvent such as N,N-diethylaniline, but the isolated yields of ketone are often low. It has been found that the best yields were obtained using ether as solvent, this solvent being far superior to tetrahydrofuran. Very low yields of ketone are generally obtained in reactions with activated nitriles, such as acetonitrile, allylnitrile and phenylacetonitrile, but these can be somewhat improved by use of a large excess of Grignard reagent.

The statement made in many organic text books that the reaction of nitriles with Grignard reagents, followed by acid hydrolysis, is a convenient method for the synthesis of ketones, is thus misleading. The possibility of condensation reactions occurring for alkyl nitriles, and how these can be minimised, should be indicated.

2.4 The Synthesis of ortho-Hydroxyphenyl Alkyl Ketones

In view of the difficulties encountered in the synthesis of the acyclic hydroxy ketones it was decided to restrict the current study to ortho-hydroxyphenyl alkyl ketones such as ortho-hydroxybutyrophenone and ortho-hydroxyvalerophenone. The former is commercially available and the latter was synthesised as shown in Scheme 28.

SCHEME 28



The overall yield of ortho-hydroxyvalerophenone was 34%. This scheme was followed in preference to the Fries rearrangement used by Dutton *et al.*[41] as the latter method has been found to give mainly para-hydroxyvalerophenone[42].

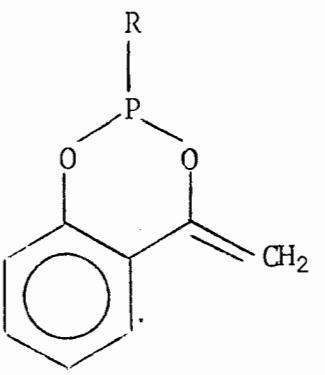
CHAPTER 3

THE SYNTHESIS OF PHOSPHORUS DERIVATIVES OF ORTHO-HYDROXYPHENYL ALKYL KETONES

CHAPTER 3

THE SYNTHESIS OF PHOSPHORUS DERIVATIVES OF ORTHO-HYDROXYPHENYL ALKYL KETONES

A standard preparation of tertiary phosphites is via the reaction of a phosphorus trihalide with an alcohol or phenol. In particular, triphenylphosphite has been synthesised in high yield from phosphorus trichloride and phenol[43]. Thus the synthesis of tertiary aryl phosphites of the type $P(OC_6H_4COR)_3$ was attempted by reaction of phosphorus trichloride with o-hydroxyacetophenone in the presence of a suitable base. Mass and ^1H n.m.r. spectral data, however, indicated the product of the reaction involving phosphorus trichloride with three-fold molar amounts of o-hydroxyacetophenone and triethylamine to be the 1,3,2-dioxaphosphorinan (25; R = o-OC_6H_4COMe) and not $P(o\text{-}OC_6H_4COMe)_3$.



(25)

There was no peak at $^m/_e$ 436 in the mass spectrum corresponding to the expected molecular ion $[P(o\text{-}OC_6H_4COMe)_3]^{\cdot+}$, but a prominent peak at $^m/_e$ 300 was in accordance with the proposed structure. The resonances in the ^1H n.m.r. spectrum at δ4,87 and 5,10 indicated the presence of an exocyclic methylene group, while a singlet at δ2,38 could be ascribed

to the acetyl group. Attempts to separate this species from unreacted ketone by fractional distillation were unsuccessful. Treatment of the impure product with either $[CpFe(CO)_2I]$ or $[Fe_2(CO)_9]$ (Scheme 29), gave reaction mixtures shown to contain the metal complexes $[CpFe(CO)(L)I]$ and $[Fe(CO)_4L]$ respectively , where L is (25; R = o-OC_6H_4COMe), on the basis of the i.r. spectra of the products (Table 3.1). Such complex formation rules out the presence of a penta-coordinate phosphorus since such compounds would not react with the iron carbonyls.

SCHEME 29

$$[CpFe(CO)_2I] + L \rightarrow [CpFe(CO)(L)I] + CO$$

$$[Fe_2(CO)_9] + L \rightarrow [Fe(CO)_4L] + Fe(CO)_5$$

L = ligand (25; R = o-OC_6H_4COMe)

Cp = cyclopentadienyl

TABLE 3.1

Complex [a]	ν(C=O) cm^{-1} [b]		
$[CpFe(CO)_2I]$	2039	1995	
$[CpFe(CO)(L)I]$	2039 [c]	1995 [c]	1970 (sh)
$[CpFe(CO)P(OPh)_3I]$	1986[44]		
$[Fe_2(CO)_9]$	2080	2034	1828[45]
$[Fe(CO)_4L]$	2081	2010	1972
$[Fe(CO)_4P(OPh)_3]$ [d]	2066	1996	1960[46]

a. L = ligand (25; R = o-OC_6H_4COMe) Cp = cyclopentadienyl

b. Spectra recorded in $CHCl_3$ or CH_2Cl_2

c. Peaks due to $[CpFe(CO)_2I]$

d. Spectrum recorded in hexane

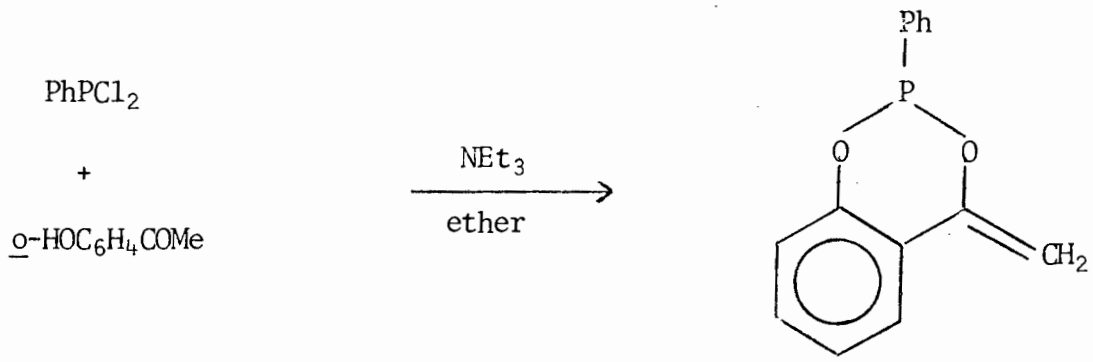
sh Shoulder

The results in Table 3.1 indicate that the reaction of the ligand with $[Fe_2(CO)_9]$ went to completion, whereas the one with $[CpFe(CO)_2I]$ did not. The i.r. spectrum of the product of the latter reaction contains peaks arising from the unreacted metal complex as well as a distinct shoulder on the 1995 cm^{-1} peak which may arise from formation of some $[CpFe(CO)(L)I]$. Although the metal complexes were not purified, their formation indicated that the phosphorus atom in the product was tri-coordinate, thus supporting the proposed structure (25; R = o-OC_6H_4COMe).

In view of the difficulties encountered in the separation of compound (25; R = o-OC_6H_4COMe) from starting material, it was decided to synthesise the 2-phenyl derivative (25; R = Ph), as this product

would be expected to have a lower boiling point and could therefore be purified by vacuum distillation. The proposed synthesis is outlined in Scheme 30.

SCHEME 30

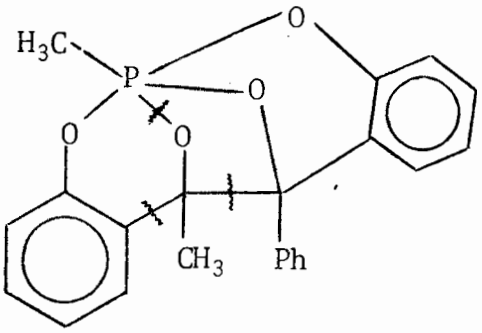


The reaction was carried out in ether using the phosphorus halide, ketone and base in the molar ratios of 1 : 1 : 2. The ^{1}H n.m.r. spectrum of the product contained, in addition to the resonances due to the aromatic hydrogens, 3 singlets at δ2,00; 1,75 and 1,55 which integrated in the ratio of 2 : 1 : 1. On standing, the product started to crystallise but attempts to purify the crystalline product failed. Use of benzene as reaction solvent, however, resulted in the isolation of the crystalline product which was purified by recrystallisation from benzene. Mass spectral data ($M^{+\cdot}$, $^{m}/_{e}$ 378) and elemental analysis indicated a molecular formula which corresponds to $PhP(OC_6H_4COMe)_2$. Other spectroscopic evidence, however, does not agree with this structure; for instance there are no peaks due to carbonyl absorptions in the i.r. spectrum, and the ^{1}H n.m.r. contains, in addition to two multiplets at

δ8,0-8,4 (2H) and 6,7-7,7 (11H) due to aryl hydrogens, a singlet at δ2,0 (3H) and two singlets at 1,75 and 1,55 integrating for a total of three hydrogens. The latter two signals were shown to correspond to a doublet at δ1,65 (J 20Hz, 3H) by recording the spectrum at both 60 and 100 MHz. Significant peaks were observed in the mass spectrum at $^{m}/_{e}$ 378, 335, 259, 243 and 165.

It is difficult to formulate a structure consistent with the above data, but the coupling of 20 Hz observed for the methyl resonance at δ1,65 is typical of a $^{2}J(PCH)$ system[47]. The structure (26) has been postulated on the basis of mass spectral and ^{1}H n.m.r. data. The fragmentation pattern is shown in Scheme 31.

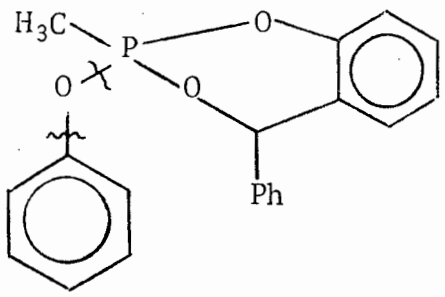
SCHEME 31



(26)

$M^{+\cdot}$ 378

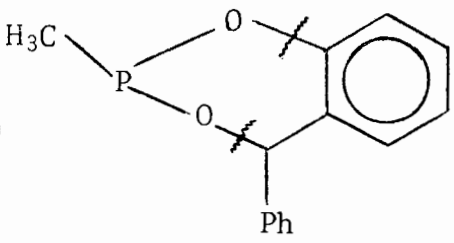
-43 (CH_3CO)



$^m/e$ 335

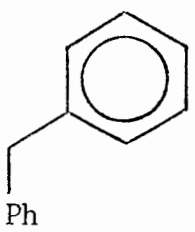
1) -76($^m/e$ 259)

2) -16($^m/e$ 243)



$^m/e$ 243

-78($^m/e$ 165)



$^m/e$ 165

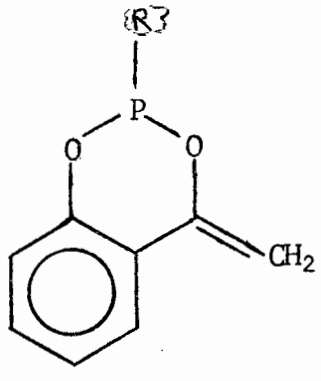
accurate mass observed 165,070 056

accurate mass calculated 165,070 421

Unfortunately it was not possible to carry out an accurate mass determination of the molecular ion due to the recorded peak being of too low intensity. Crystals have been submitted for X-ray crystallographic studies but, as yet, no results are available. The same product has subsequently been isolated from reactions carried out in ether using

either triethylamine or pyridine as a base.

Attention was once again focussed on the 1,3,2-dioxaphosphorinan formed by reaction of phosphorus trichloride with o-hydroxyacetophenone. It was anticipated that if the ketone was added very slowly and in dilute solution to the phosphorus trichloride and base it might be possible to isolate the 2-chloro derivative (25; R = Cl)

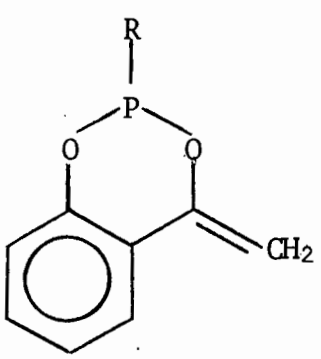


(25)

Reaction using a 5% excess of phosphorus trichloride gave a product shown by ^{1}H n.m.r. to be an equimolar mixture of the desired 2-chloro derivative (25; R = Cl) and the o-hydroxyacetophenone derivative (25; R = o-OC_6H_4COMe) together with unreacted ketone. The ^{1}H n.m.r. spectrum contained, in addition to resonances due to aryl protons, multiplets at δ4,87, 5,10 and 5,26 with intensities in the ratio of 2 : 1 : 1; those at δ4,87 and 5,10 being due to (25; R = o-OC_6H_4COMe) and those at δ4,87 and 5,26 being due to (25; R = Cl). There was a singlet at δ2,38 due to the acetyl group of (25; R = o-OC_6H_4COMe). Use of a 50% excess of phosphorus trichloride gave a mixture of (25; R = Cl) and unreacted o-hydroxyacetophenone. Attempted separation by fractional distillation led only to the recovery of the o-hydroxyketone, the residue solidifying in the distillation flask.

Repetition of the reaction using a 100% excess of phosphorus trichloride, followed by distillation, gave a small amount of pale yellow liquid which was stored under nitrogen. The ^{1}H n.m.r. spectrum was consistent with the proposed structure (25; R = Cl), having resonances at δ7,26 due to the aryl hydrogens and at δ4,87 and 5,26 due to the exocyclic methylene group hydrogens; very weak signals due to traces of o-hydroxyketone and (25; R = o-OC_6H_4COMe) were also present. Variation of the reaction conditions led to an optimum yield of the product being obtained when phosphorus trichloride, triethylamine and o-hydroxyacetophenone were reacted together in the molar ratio of 2,5 : 2,5 : 1. The 2-chloro-1,3,2-dioxaphosphorinan (25; R = Cl) was found to be very sensitive to both moisture and air, turning red and solidifying when exposed to the atmosphere. Great care was thus exercised during its preparation to exclude air and moisture.

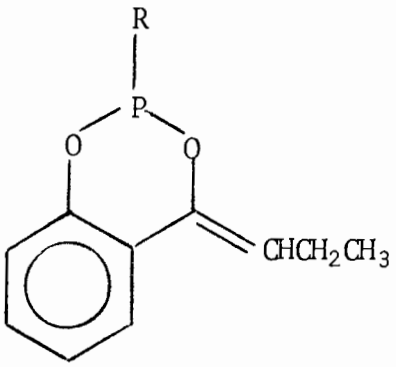
It was reasoned that the 2-alkoxy and 2-phenoxy derivatives of (25) might be less labile and easier to characterise than (25; R = Cl). Thus a series of compounds of type (25; R = alkoxy or phenoxy groups) was prepared by reaction of (25; R = Cl) with the appropriate alcohol in the presence of triethylamine.



(25)

R = OMe, OPr^i, OBu^t, OCH_2Ph and OPh.

The reaction was also carried out using o-hydroxybutyrophenone as substrate, and compounds of type (27; R = Cl, OMe) were obtained.



(27)

These compounds were characterised by elemental analysis as well as by i.r. and 'H n.m.r. spectroscopy and accurate mass determination of the molecular ions. The absence of peaks between 1650 and 1750 cm^{-1} due to the carbonyl group in the i.r. spectra of these compounds is consistent with the proposed structures (25 and 27). The 'H n.m.r. spectral data of the 1,3,2-dioxaphosphorinans are given in Table 3.2.

TABLE 3.2

	Compound	Chemical shift (p.p.m) (J in Hz)			
		= CHR' [a]		Aryl H	R group H
25	1) R = Cl	4,87	5,26	6,9 - 7,7 m	
	2) R = OMe	4,74	5,03	6,9 - 7,8 m	CH_3: 3,62 d (11)
	3) R = OPr^i	4,70	5,03	6,8 - 7,6 m	CH: 4,50 m [b] CH_3: 1,22 t (6) [c]
	4) R = OBu^t	4,66	5,02	6,8 - 7,6 m	CH_3: 1,39 s
	5) R = OCH_2Ph	4,71	5,02	6,8 - 7,6 m	CH_2: 4,93 d (9)
	6) R = OPh	4,82	5,12	6,9 - 7,8 m	
27	7) R = Cl	=CH:	5,72 t (7)	6,9 - 7,7 m	
		CH_2:	2,29 pent (7)		
		CH_3:	1,07 t (7)		
	8) R = OMe	=CH:	5,48 t (7)	6,8 - 7,5 m	CH_3: 3,60 d (11)
		CH_2:	2,32 pent (7)		
		CH_3:	1,07 t (7)		

a. Signals for $=CH_2$ appear as broad singlets ($W_{\frac{1}{2}}$ 4Hz).
R' = H for compounds (25) and Et for compounds (27).

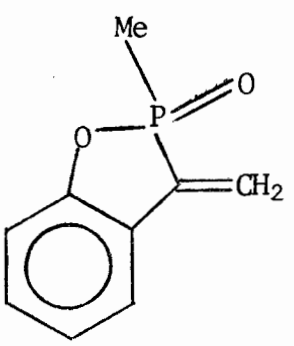
b. Signal collapses to a doublet (J 9Hz) on irradiation at δ1,22.

c. Signal collapses to a doublet (J 6Hz) on irradiation at δ4,50.

The line broadening ($W_{\frac{1}{2}}$ 4Hz) observed for the exocyclic methylene hydrogen signals of the compounds (25; Entries 1-6) indicates weak ^4J(POC=CH) coupling of these protons to the phosphorus[48], while, in the case of the products (27; R = Cl, OMe, Entries 7 and 8) the olefinic proton signal appears as a triplet (J 7Hz), further split by coupling

to the phosphorus (J 2Hz). Relatively strong coupling (J 9-11Hz) was observed for protons attached to carbon which is in turn linked to phosphorus via oxygen[49] i.e. a $^3J(POCH)$ system (Entries 2,5 and 8). The triplet observed for the methyl groups in compound (25; R = OPr^i, Entry 3) might arise from equal coupling of the methyl groups to the α-hydrogen and phosphorus, or could be due to overlapping doublets of two non-equivalent methyl groups.

Reaction of (25; R = OMe) with $[CpFe(CO)_2I]$ (cp = η-C_5H_5) in refluxing benzene afforded a single product purified by column chromatography, the spectroscopic data of which are consistent with it being $[CpFe(CO)(MeO\overline{POC_6H_4COCH_2})I]$ [ν(C=O) 1977 cm^{-1} in CH_2Cl_2; δ 4,36 and 5,13 (d J 2Hz, = CH_2), 4,34 (s, C_5H_5), 3,76 (d J 11,6Hz, OMe)][50]. The formation of this complex provides support for structure (25; R = OMe) as opposed to the other possible structure (28), since the latter ligand would not be expected to give rise to a stable substituted derivative of $[CpFe(CO)_2I]$.

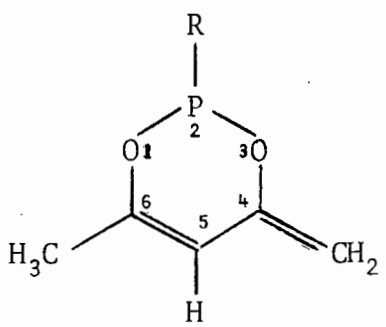


(28)

Further evidence against structure (28) is the absence of any band corresponding to P=O in the i.r. spectra of the products. Treatment of compounds (25; R = OMe, OPh) in deuterochloroform with anhydrous

hydrogen chloride regenerated the ketone fragment, o-OC_6H_4COMe as indicated by the disappearance of the resonances due to the exocyclic methylene group, and the appearance of a singlet at δ2,60 due to the acetyl group of the ketone, in the 'H n.m.r. spectra.

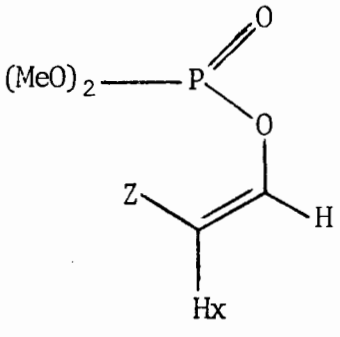
Although there is no n.m.r. evidence for the presence of the enol tautomer of o-HOC_6H_4COR in solution, (25 and 27; R = Cl) may formally be considered as having been formed from o-$HOC_6H_4C(OH)=CHR$ by proton abstraction from the two hydroxy groups. Attempts were thus made to establish whether an analogous dioxaphorphorinan could be formed by the reaction of phosphorus trichloride and acetylacetone in the presence of triethylamine. Reaction under similar conditions to those used previously, did, indeed, afford a product proposed to be the 2-chloro derivative (29; R = Cl)



(29)

on the basis of 'H n.m.r. evidence [δ5,50 (d J 3Hz, 5-H), 4,50 and 4,35 (br s, $=CH_2$), 1,92 (s, Me)]. Treatment of (29; R = Cl) with methanol in the presence of triethylamine afforded an unstable product ($^{m}/_{e}$ 160) postulated to be the 2-methoxy derivative, (29; R = OMe), on the basis of 'H n.m.r. evidence [δ5,38 (d J 3Hz, 5-H), 4,34 and 4,12 (br s, $=CH_2$), 3,65 (d J 11Hz, OMe) and 1,90 (s, Me)]. The coupling of

3Hz observed between the ^{31}P and 5-H in (29; R = Cl, OMe) is similar to that observed by Gaydou[48] for $^{4}J(POC=CH)$ in *transoid* enolic phosphates of the type (30)



(30)

Z	$^{4}J(POC=CH_x)$ in Hz
H	2,85
CH_3	2,33
Cl	1,75

The signals due to the exocyclic methylene hydrogens, however, appear as broad singlets ($W_{\frac{1}{2}}$ 4Hz) indicating weak coupling of these protons to the phosphorus. This is similar to the line broadening observed for the exocyclic methylene hydrogen signals for compounds (25 and 27, see Table 3.2).

The formation of dienolate anions has been invoked in the treatment of β-diketones with strong bases [51] as shown in Scheme 32.

SCHEME 32

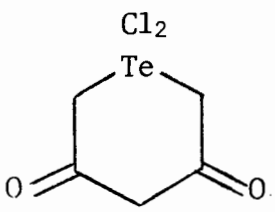
$$CH_3COCH_2COCH_3 \xrightarrow[\text{ether, } -78^{\circ}C]{NaNH_2/\text{liq } NH_3} CH_3C(O^-)=CH-C(O^-)=CH_2 \; 2Na^+$$

1) $n\text{-}C_4H_9Br$ (1 equiv)
liq NH_3, ether
$\longrightarrow$ $CH_3COCH_2COCH_2C_4H_9{}^n$

2) HCl, H_2O

81-82%

The isolation of a dienolic β-diketone derivative has, however, as far as can be determined, not previously been reported. In this respect, the reactions of acetylacetone with BCl_3, $AlCl_3$ and $SiCl_4$ have been shown to afford $[B(acac)_2]^+$, $[Al(acac)_3]$ and $[Si(acac)_3]^+$ (acac = acetylacetonate) respectively, with no α-hydrogen abstraction being reported[52]. Reaction of $TeCl_4$ with acetylacetone in $CHCl_3$ yields a compound formulated as $TeCl_2 \cdot C_5H_6O_2$ (31), a derivative of 1-telluracyclohexane-3,5-dione[53].



(31)

A reaction analogous to that between dichloro phenylphosphine and o-hydroxyacetophenone in the presence of base (Scheme 30) was carried out using dichloro phenoxyphosphine instead of dichloro

phenylphosphine in order to observe the influence of the organic moiety of the phosphorus halide on the course of the reaction. The ^{1}H n.m.r. of the crude product [δ 6,9-7,8 (m, ArH), 5,12 and 4,82 (br s, $=CH_2$), 2,60 (s, CH_3)] indicated that the product was a mixture of o-hydroxyacetophenone and (25; R = OPh). Crystals formed in the crude product, but they could not be purified and characterised. The formation of the 2-phenoxy-1,3,2-dioxaphosphorinan (25; R = OPh) suggests that the reactivity of dichloro phenoxyphosphine parallels that of phosphorus trichloride more than that of dichloro phenylphosphine.

It is apparent from the above studies that the reaction of o-hydroxyphenyl alkyl ketones with phosphorus trichloride and dichloro phenylphosphine do not yield compounds suitable for photochemical studies, for which compounds of the type $P(o\text{-}OC_6H_4COR)_3$, (R = Pr^n and Bu^n) are required. Thus, o-hydroxyacetophenone was reacted with chloro diphenylphosphine in the molar ratio of 1,1 : 1 to form $Ph_2P(o\text{-}OC_6H_4COMe)$. ^{1}H n.m.r. and i.r. spectral data indicated that a mixture containing the hydroxyketone and the desired product in the ratio of 1 : 3 was obtained. Attempts to separate the ligand from the starting ketone were unsuccessful. Reaction of the impure ligand with $[CpFe(CO)_2I]$ and $[Fe_2(CO)_9]$ (see Scheme 29 and Table 3.1) gave mixtures containing the metal complexes $[CpFe(CO)(L)I]$ and $[Fe(CO)_4L]$, L = $Ph_2P(o\text{-}OC_6H_4COMe)$ as indicated by their i.r. spectra (Table 3.3).

TABLE 3.3

Complex	ν(C=O) cm^{-1} a		
[CpFe(CO)(L)I]	2039 b	1995 b	1972
[$Fe(CO)_4L$]	2061	1990	1952

L = $Ph_2P(o\text{-}OC_6H_4COMe)$

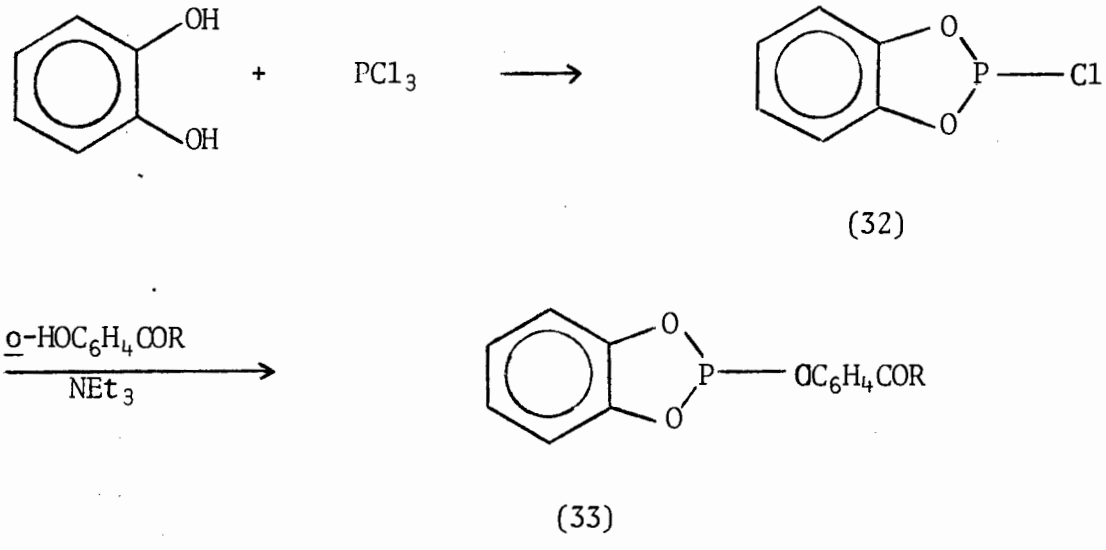
a. Spectra recorded in $CHCl_3$

b. [$CpFe(CO)_2I$]

As in the case of (25; R = OC_6H_4COMe) the results indicate that the reaction of the ligand with [$Fe_2(CO)_9$] proceeds to completion whereas that with [$CpFe(CO)_2I$] does not. The metal complexes were not purified but their formation indicates that the phosphorus atom of the ligand is tri-coordinate. Repetition of the reaction using different molar ratios of hydroxyketone to chloro diphenylphosphine and base still gave mixtures of the desired product and starting ketone which resisted all attempts at separation.

The incomplete reaction of o-hydroxyacetophenone with chloro diphenylphosphine might possibly be ascribed to the lower reactivity of this phosphorus halide compared to phosphorus trichloride or dichloro phenylphosphine. o-Phenylene phosphorochloridite (32) was reacted with o-hydroxyacetophenone under a variety of conditions in the hope that the reaction would go to completion, but, once again, inseparable mixtures of the desired product and starting material were obtained. Similar results were obtained using (32) and o-hydroxybutyrophenone (Scheme 33).

SCHEME 33



[R = Me, Pr^n]

Despite the inability to prepare phosphorus derivatives of o-hydroxyphenyl alkyl ketones suitable for the photochemical studies envisaged in Chapter 1 (see Scheme 16), the investigations discussed above have resulted in the development of some novel phosphorus chemistry[54]. The product of the reaction of o-hydroxyacetophenone with dichloro phenylphosphine (pages 34-38) appears to possess a novel structure not previously encountered in phosphorus chemistry, and this reaction will be the subject of further studies. Finally, suitable phosphorus-containing ligands are formed in the reaction of o-hydroxyphenyl alkyl ketones with chloro diphenylphosphine and o-phenylene phosphorochloridite (32), and it is to be hoped that the difficulties encountered in the separation of these products from starting material will be overcome in future studies.

CHAPTER 4

EXPERIMENTAL

CHAPTER 4

EXPERIMENTAL

Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. I.r. spectra were measured for liquid films (unless otherwise stated) on a Perkin Elmer Model 237 Grating Spectrometer. In recording the results s refers to a strong, m refers to a medium and w refers to a weak absorption. ^{1}H n.m.r. spectra were measured for solutions in [^{2}H]-chloroform on a Varian XL 100 instrument using tetramethylsilane as an internal standard. In the n.m.r. spectra all signals ascribed to replaceable protons disappeared on shaking with D_2O. Mass spectra were recorded on a Varian MAT Mass Spectrometer MAT 311A at Stellenbosch University. T.l.c. was carried out using Merck D.C. Kieselgel F254 plates and a solvent system consisting of 40% ethyl acetate in pet. ether. Pet. ether refers to the fraction which boils between 60 and 80°. G.l.c. was carried out on a PYE series 104 Gas Chromatograph. The column consisted of 10% carbowax 20M on 80-100 mesh chromosorb W (H.P.). Microanalyses were carried out at the University of Cape Town by Mr. Hemstead. All reactions in which Grignard reagents or phosphorus compounds were prepared were carried out in an atmosphere of dry nitrogen. Pyridine and triethylamine were distilled from KOH pellets and stored over KOH. Anhydrous Na_2SO_4 was used for drying ethereal solutions. Ether and THF were dried over sodium wire and distilled from NaH. All alcohols and alkyl and aryl bromides were purified by distillation and stored over molecular sieves. Phosphorus halides were freshly distilled before being used in reactions.

Synthesis of Hydroxy Ketones

Butyl magnesium bromide

The preparation of butyl magnesium bromide is given as a typical synthesis of a Grignard reagent. To 2,64g (0,11 mol) Mg in a 250 ml 3-necked flask fitted with a condenser, a stirrer and a pressure equilibrating dropping funnel was added 10 ml ether. A small amount of a solution of 13,7g (0,1 mol) 1-bromobutane in 20 ml ether as well as a few crystals of iodine was added to the Mg. Once the reaction had been initiated, the remainder of the 1-bromobutane in ether was added dropwise with stirring so that the solution boiled gently. If the reaction became too vigorous the flask was cooled in an ice bath. After the addition was complete the mixture was heated under reflux for 15 minutes. The Grignard reagent was then reacted with the substrate and the addition product decomposed using either a saturated solution of NH_4Cl or dilute acid. Crushed ice was used to control the rate of the reaction. The ether layer was separated and the aqueous layer extracted 3 or 4 times with ether. The combined ether extracts were washed with 10% Na_2CO_3 solution and water and dried over Na_2SO_4. After filtering the ether was removed under reduced pressure.

1-Hepten-4-ol (19; R = Pr^n)

85g (3,5 mol) Mg in 600 ml ether and a few crystals of iodine were placed in a flask. 140g (1,16 mol) allyl bromide in 100 ml ether was added dropwise over 6 hours (a slow rate of addition is needed to cut down the extent of coupling reactions). The solution was stirred for a further 1½ hours at r.t.[55] The allyl magnesium bromide was filtered through glass wool into a dry flask. A solution of 72,5g (1,0 mol)

n-butanal in 90 ml ether was then added over $2\frac{1}{2}$ hours to the stirred solution of allyl magnesium bromide cooled in an ice bath. Once the addition was completed the mixture was heated under reflux for 1 hour and then cooled. The Grignard addition product was hydrolysed by addition of crushed ice and 200 ml dilute HCl. The ether layer was separated and washed with water (3 x 200 ml), 200 ml 10% Na_2CO_3 solution and 200 ml water. The ethereal solution was dried over Na_2SO_4. Filtration and removal of the solvent under reduced pressure yielded 101g crude product. The alcohol was purified by distillation, $b.p._{51}$ 84-87° (lit. $b.p._{20}$ 61° [56]). 81,15g (71%) was obtained, ν_{max} 3600-3280, 1640 cm^{-1}, δ 5,62-6,04 (m, 1H, 2-H), 5,0-5,2 (m, 2H, $=CH_2$), 3,55-3,80 (m, 1H, 4-H), 2,21 (s, 1H, OH), 2,18-2,26 (m, 2H, 3-H), 1,35-1,50 (m, 4H, 5- and 6-H), 0,95 (t J 7Hz, 3H, Me).

Attempted Synthesis of 1-hepten-4-one (20; R = Pr^n)

a) Using chromic acid/ether[30]

10 ml ether and 2,24g (20 mmol) alcohol (19; R = Pr^n) were placed in a 100 ml flask fitted with a stirrer, a condenser and a dropping funnel. 10 ml (20 mmol) chromic acid solution (prepared by dissolving 10g (0,033 mol) $Na_2Cr_2O_7 \cdot 2H_2O$ in 30 ml water, adding 13,6g (0,134 mol) 97% H_2SO_4, and diluting the solution to a total volume of 50 ml) was added to the stirred solution of the alcohol over 15 minutes. The temperature was maintained at 25-30°. During the addition the solution became warm and turned brown. After stirring at r.t. for $3\frac{1}{4}$ hours the ether was separated and the aqueous phase extracted with two 10 ml portions of ether. The combined ether extracts were washed with saturated Na_2CO_3 solution and then water. The ether extracts were

dried over Na_2SO_4, filtered, and the ether was removed under reduced pressure. 1,56g of crude product was obtained. This product was a mixture of alcohol and ketone, ν_{max} 3560-3100, 1710, 1640 cm^{-1}. The n.m.r. spectrum of the mixture contained, in addition to peaks due to 1-hepten-4-ol (as described earlier), peaks due to the ketone at δ 5,66-6,08 (m, 1H, 2-H), 5,0-5,22 (m, 2H, $=CH_2$), 3,18 (d J 6Hz, 2H, 3-H), 2,44 (t J 6Hz, 2H, 5-H), 1,58-1,76 (m, 2H, 6-H), 0,92 (t J 7Hz, 3H, Me).

Similar oxidation using 1,14g (10 mmol) alcohol (19; R = Pr^n) and 5,5 ml (11 mmol) chromic acid solution at -18^o likewise gave a mixture of alcohol and ketone (0,7g).

1,14g (10 mmol) of alcohol (19; R = Pr^n) and 10 ml (20 mmol) of chromic acid solution were reacted together as described previously. 0,77g crude ketone (20; R = Pr^n) was isolated, ν_{max} 1710, 1640 cm^{-1}.

11,4g (100 mmol) of alcohol (19; R = Pr^n) and 100 ml (200 mmol) of chromic acid solution were reacted together as described previously to give 8,55g of a mixture of alcohol and ketone. Distillation of the mixture ($80-86^o$, 50mm Hg) failed to separate the two compounds, while distillation at atmospheric pressure gave a product containing the alcohol and the α,β- unsaturated ketone, $CH_3CH_2CH_2COCH=CHCH_3$, ν_{max} 3600-3300(w), 1676, 1640 cm^{-1}, the n.m.r. spectrum contained, in addition to peaks due to the alcohol, peaks at 6,66-6,94 (dxq J 7 and 16Hz, 1H, 2-H), 5,12 (d J 16Hz, 1H, 3-H), 2,43 (t J 6Hz, 2H, 5-H), 2,04-2,22 (m, 2H, 6-H), 1,90 (d J 7Hz, 3H, 1-H), 0,92 (t J 7Hz, 3H, 7-H).

b) Using chromic acid/3,5-dimethylpyrazole[31]

5,8g (60 mmol) 3,5-dimethylpyrazole (prepared according to the literature procedure [57]) was added to a suspension of 6,0g (60 mmol) CrO_3 in 85 ml CH_2Cl_2 and the mixture was stirred at r.t. under nitrogen for 15 minutes. To the resulting dark red solution 2,51g (22 mmol) of alcohol (19; R = Pr^n) in 10 ml CH_2Cl_2 was added in one portion and the reaction mixture was stirred at r.t. for 30 minutes. The solvent was removed under reduced pressure, the brown residue was extracted with several portions of ether and the resulting mixture was filtered. Removal of the ether yielded 0,3g crude product, ν_{max} 3610-3050, 1710, 1640 cm^{-1}.

Attempted Synthesis of 1-hydroxy-4-octanone (Scheme 18)

Butyl magnesium bromide (0,05 mol) prepared according to the procedure described earlier was filtered through glass wool into a clean dry dropping funnel and added dropwise with stirring at 0^o to 8,61g (0,1 mol) γ-butyrolactone. After the addition was complete the mixture was stirred at 0^o for 1 hour and dilute HCl was then added slowly until a clear solution was obtained. The layers were separated, the aqueous layer was extracted twice with ether and the combined ether extracts were washed with water, 10% Na_2CO_3 solution (the yellow colour disappeared) and water. After drying over Na_2SO_4 and filtering, the ether was removed to give 3,23g of the crude product, ν_{max} 3390, 1740 (ester), 1720 cm^{-1} (ketone).

The reaction was repeated following the same procedure as above except that the reaction mixture was stirred at r.t. for 1 hour. 5,5g of crude material was obtained, ν_{max} 1780 (lactone), 1740 (ester) and 1720 cm^{-1} (ketone).

Reaction of butyl magnesium bromide (0,1 mol) with 8,61g (0,1 mol) γ-butyrolactone at r.t. for 2 hours, followed by a similar work-up procedure to that described above, gave 5,72g crude product. G.l.c. analysis indicated that the product contained 5 components, 4 having relatively short retention times, $t_R \leqslant$ 4 minutes, and one of longer retention time, t_R 11,5 minutes. None of the components corresponded to either the lactone or 1-bromobutane.

Similar reaction using a molar ratio of butyl magnesium bromide to γ-butyrolactone of 0,1 to 0,09 gave 8,27g of product, ν_{max} 3390(s), 1780 and 1770 (w), 1740(s), 1720(m) cm^{-1}. G.l.c. analysis indicated that the product was a mixture of 7 components; 5 having relatively short retention times, $t_R \leqslant$ 8 minutes, including 1-bromobutane and γ-butyrolactone, and two components of longer retention time, t_R 16,4 and 23,3 minutes. Reasonable separation of the components was obtained by t.l.c. on silica using 2,5% ethanol in chloroform as developing solvent. An attempt to separate the components by column chromatography on silica, however, failed.

Repetition of the reaction on a larger scale using butyl magnesium bromide (0,5 mol) and γ-butyrolactone (0,5 mol) gave 37,7g of crude product which was distilled under reduced pressure. Two fractions were obtained. The first fraction (4,3g; $b.p._{0,5}$ 20-100°) was shown by g.l.c. analysis to contain 5 components one of them being γ-butyrolactone. The second fraction ($b.p._{0,5}$ 104-120°) consisted of 21,23g (20%) of a single product (as indicated by g.l.c. analysis) which was shown to be the diol (22). M^+, $^m/_e$ 202; ν_{max} 3350 cm^{-1}; δ 3,70 (br s, 2H, OH), 3,58 (t J 6Hz, 2H, 3-H), 1,20-1,58 (m, 16H, 8xCH_2), 0,91 (t J 6Hz, 6H, Me). The residue from the distillation (2,35g) consisted of several components

as indicated by g.l.c. analysis, one of the components being the diol (22).

Repetition of the reaction on the same scale, but at -45^{o}, gave 37,0g of crude product. Distillation gave three fractions, the first (6,11g; $b.p._{2,0}$ $46-86^{o}$) consisting mainly of unchanged lactone. The second fraction (14,07g; $b.p._{2,0}$ $86-114^{o}$) consisted of one major component (by g.l.c. analysis) in addition to a small amount of diol (22). This major component [alkenol (23)] was not present in the crude reaction mixture and must have been formed during the distillation. The third fraction (3,93g; $b.p._{3,0}$ $134-150^{o}$) consisted of a mixture of products as indicated by g.l.c. analysis; two of the components were the diol (22) and the alkenol (23). The 2,07g of residue from the distillation contained mainly the diol (22). 1g of the diol (22) in $CHCl_3$ was heated under reflux for $1\frac{1}{4}$ hours, and another sample containing 1g diol and 2 drops HCl in $CHCl_3$ was also heated under reflux for $1\frac{1}{4}$ hours. In both cases the alkenol (23) was obtained, ν_{max} 3380, 1660 cm^{-1}, δ 5,0-5,24 (m, 1H, 3-H), 3,61 (t J 6Hz, 2H, 1-H), 2,66 (br s, 1H, OH), 1,95-2,10 (m, 6H, 3xallylic CH_2), 1,22-1,50 (m, 8H, 4xCH_2), 0,91 (t J 6Hz, 6H, Me).

Attempted Synthesis of 1-octen-4-one (Scheme 21)

22,36g (0,30 mol) allyl cyanide was added dropwise to butyl magnesium bromide (0,36 mol) in ether cooled in an ice bath. The addition product was hydrolysed using ice and dilute H_2SO_4, large amounts of gummy material being formed; no attempt was made to characterise the gum.

Separation of the ether layer and normal work-up procedure gave 4,35g of product, ν_{max} 3350 cm^{-1}.

2-Hexanone

Dropwise addition of 12,32g (0,30 mol) acetonitrile to butyl magnesium bromide (0,36 mol) in ether, followed by hydrolysis of the product with ice and dilute H_2SO_4 (100 ml), gave 6,33g of crude product, ν_{max} 1712 cm^{-1}. The ketone was distilled yielding 3,8g (13,5%) b.p.$_{760}$ 112-114^{o} (lit. 128^{o} [58]); n.m.r. indicated the presence of significant amounts of impurities.

5-Nonanone

6g (0,072 mol) of pentanenitrile (prepared from 1-bromobutane and NaCN in DMSO[59]) was added dropwise to butyl magnesium bromide (0,08 mol) in ether at 0^{o} and then the mixture was heated under reflux for 3½ hours. A green syrupy substance formed. The addition product was decomposed by careful addition of saturated NH_4Cl solution. Normal work-up gave 8g of crude product, ν_{max} 3385, 2195, 1710, 1640 cm^{-1} (peaks at 1710 and 1640 cm^{-1} were approximately equal in intensity). Stirring of the product (1,0g) in ether (5 ml) with dilute H_2SO_4 (1 ml) for ½ hour, or refluxing of a THF solution (1g in 3 ml) with water (3 ml) for 3½ hours gave a product in which the peak at ν_{max} 1710 cm^{-1} increased in intensity at the expense of that at 1640 cm^{-1}.

Replacement of ether by THF as solvent in the above procedure gave 8,0g of crude product, ν_{max} 3385, 2195, 1640 cm^{-1}. Treatment of the product in ether with dilute H_2SO_4 or refluxing of a THF solution with

water as above gave a product exhibiting a peak at 1710 cm^{-1}.

Repetition of the reaction in ether but this time refluxing the mixture for 5 hours, gave 6,35g of crude product, ν_{max} 3385, 2195, 1710, 1640 cm^{-1}. T.l.c. analysis of the product and visualisation of the plate with iodine indicated the presence of two main components (probably 5-nonanone and the corresponding imine) with little unchanged nitrile being detected.

Repetition of the reaction in THF using butyl magnesium bromide (0,064 mol) and pentanenitrile (0,057 mol) and refluxing the mixture for 5 hours gave 5,82g of crude product. Vacuum distillation gave 1g of the α-cyano-imine (24), a pale yellow liquid b.p.$_{0,5}$ 101°. Found: C 72,2; H 10,6; N 15,7; $C_{10}H_{18}N_2$ requires C 72,2; H 10,9; N 16,8%. M^+, m/e 166, ν_{max} 3385, 2195, 1640 cm^{-1}. δ 4,58 (br s, 1H, NH), 4,58 (s, 1H, -CHCN), 2,42 (t J 7Hz, 2H, $-CH_2\underset{|}{C}=NH$), 1,92-2,08 (m, 2H, $-CH_2CHCN$), 1,20-1,64 (m, 6H, 3xCH_2), 0,96 (t J 7Hz, 3H, Me), 0,94 (t J 7Hz, 3H, Me).

4-Octanone[39]

Propyl magnesium bromide (0,11 mol) was prepared in ether and, after addition of 74,60g (0,5 mol) $PhNEt_2$, the ether was removed under reduced pressure. 8,31g (0,10 mol) Pentanenitrile was added dropwise keeping the temperature at 70°. The homogeneous solution was stirred for 1 hour at 70° and then left to stand at r.t. overnight. After addition of dilute H_2SO_4 the aqueous layer was extracted 4 times with ether and the combined ether extracts were washed with 10% Na_2CO_3 solution

and water and dried over Na_2SO_4. Removal of the ether yielded 8,82g of crude product, ν_{max} 2265, 1722, 1715 cm^{-1}. G.l.c. analysis indicated that the mixture contained 4-octanone, $PhNEt_2$, 1-bromopropane and a trace of 5-nonanone. Distillation gave 4,70g (37%) of 4-octanone, b.p.$_{760}$ 166-170°, (lit. 170° [60]), ν_{max} 1715 cm^{-1}, δ 2,40 (t J 7Hz, 4H, 3- and 5-H), 1,20-1,72 (m, 6H, 2-, 6- and 7-H), 0,92 (t J 7Hz, 6H, Me). G.l.c. analysis indicated that the ketone was pure.

The reaction was carried out again as above but the $PhNEt_2$ was omitted and the addition product was hydrolysed using a saturated solution of NH_4Cl followed by 0,1M H_2SO_4. 10g of crude product was isolated, ν_{max} 3385, 2195, 1715 cm^{-1}. Distillation yielded 6,53g (51%) 4-octanone b.p.$_{760}$ 166-170° (lit. 170° [60]). M^+, $^m/_e$ 128, ν_{max} 1715 cm^{-1}; n.m.r. as for the above reaction.

Attempted Synthesis of 1-hydroxy-3-hexanone (Scheme 23; R = Pr^n)

Propyl magnesium bromide (0,2 mol) in $PhNEt_2$ (59,68g; 0,4 mol) was prepared as in the case of 4-octanone. 7,1g (0,1 mol) 3-hydroxypropanenitrile was added dropwise to the solution at 70° and a yellow solid formed. After the addition was complete the temperature was maintained at 70° for 1 hour. Addition of dilute H_2SO_4 resulted in a vigorous reaction to give an orange solution and some polymeric material. The solution was extracted several times with ether, the ether extracts were washed with Na_2CO_3 solution and water; removal of the ether under reduced pressure gave 5,0g of product, ν_{max} 3410, 1718 cm^{-1}. G.l.c. analysis indicated the presence of several components including $PhNEt_2$.

3-Hydroxy-1-propanenitrile tetrahydropyranyl ether[61]

Two drops of concentrated HCl were added to a mixture of freshly distilled dihydropyran (8,4g; 0,1 mol) and 3-hydroxy-1-propanenitrile (7,1g; 0,1 mol) with cooling, and the mixture was shaken occasionally over a period of 7 hours. After addition of a further 0,84g (0,01 mol) of dihydropyran, ether was added and the mixture was washed twice with 0,1M NaOH and once with water. The ethereal solution was dried over Na_2SO_4, filtered and the ether was removed under reduced pressure. Vacuum distillation yielded 2 fractions. The first, 1,59g, b.p.$_{21,5}$ 136-140°, was shown by g.l.c. analysis to contain unchanged nitrile, dihydropyran and the desired tetrahydropyranyl ether. The second, 10,38g (67%), b.p.$_{21,5}$ 140°, was a mixture consisting predominantly of the desired tetrahydropyranyl ether, ν_{max} 2260 cm^{-1}, δ 4,68 (t J 3Hz, 1H, 2'-H), 3,80-4,00 (m, 4H, 3'- and 6'-H), 3,72 (t J 6Hz, 2H, 3-H), 2,66 (t J 6Hz, 2H, 2-H), 1,45-2,04 (m, 4H, 4'- and 5'-H).

Addition of 10,38g of the above tetrahydropyranyl ether (0,06 mol) to propyl magnesium bromide (0,072 mol) in $PhNEt_2$ (21,49g; 0,144 mol) at 70° gave a mixture which solidified. After heating at 70° for 1 hour, the mixture was divided into 2 portions. One portion was treated with saturated NH_4Cl solution and the other with 1M H_2SO_4, but in both cases polymeric material formed and only $PhNEt_2$ was recovered on distillation.

1-Phenyl-1-pentanone (n-valerophenone)

8,31g (0,1 mol) pentanenitrile was added dropwise with stirring

to a refluxing solution of phenyl magnesium bromide (0,11 mol) in ether. The mixture was then heated under reflux for 1 hour and, after standing overnight, the addition product was decomposed using a saturated solution of NH_4Cl followed by 0,1M H_2SO_4 to give 15,14g of crude ketone, ν_{max} 1692 cm^{-1}. Distillation yielded 11,64g (71%) of the desired ketone, b.p.$_{22}$ 150-153° (lit.^{60} 242°), ν_{max} 1692 cm^{-1}, δ 7,28-7,68 and 7,90-8,00 (m, 5H, ArH), 3,0 (t J 7Hz, 2H, 2-H), 1,34-1,86 (m, 4H, 3- and 4-H), 1,0 (t J 7Hz, 3H, Me).

2-Methoxybenzaldehyde

207,32g (1,5 mol) K_2CO_3 was placed in a 2l 3-necked flask fitted with a condenser and a mechanical stirrer. A solution of 122,12g (1,0 mol) o-hydroxybenzaldehyde in 450 ml DMF (both freshly distilled) was added to the K_2CO_3 with continuous stirring to prevent coagulation. 189,2g (1,5 mol) of dimethylsulphate was then added dropwise with stirring under nitrogen. After stirring for 20 hours t.l.c. showed that the reaction had gone to completion and the mixture was filtered and the K_2CO_3 thoroughly washed with ether. The solvents were removed under reduced pressure. About 200 ml of water was added and the mixture was extracted several times with ether after adding NaCl to salt out any product in the aqueous layer. The combined ether extracts were washed successively with a concentrated ammonia solution, water and brine and dried over Na_2SO_4. The ether was removed under reduced pressure and the product distilled to give 2-methoxybenzaldehyde (101,56g; 75%), b.p.$_{14}$ 131-132° (lit.^{60} 243-246°), ν_{max} 1700 cm^{-1}, δ 10,45 (s, 1H, CHO), 6,90-7,90 (m, 4H, ArH), 3,95 (s, 3H, OMe).

1-(2'-methoxyphenyl)-1-pentanol

22,71g (0,934 mol) dry Mg turnings were placed in a dry 3-necked flask. The apparatus was flushed with a stream of dry nitrogen and 121,93g (0,89 mol) 1-bromobutane in 100 ml ether was added dropwise with stirring. After the addition, the mixture was heated gently under reflux for 1 hour. 100,64g (0,74 mol) of 2-methoxybenzaldehyde in ether was added dropwise to the butyl magnesium bromide solution with stirring, after which the mixture was heated under reflux for 1 hour. A sample of the product was withdrawn, some dilute HCl was added and t.l.c. of the organic phase indicated that the reaction had gone to completion. 200g crushed ice was added, followed by the slow addition of dilute HCl. As the reaction became less vigorous concentrated HCl was added until no further reaction occurred. The ether layer was separated and the aqueous layer was extracted twice with 100 ml ether. The combined ether extracts were washed with 3 150 ml portions of water, once with 150 ml 10% Na_2CO_3 solution and once with 150 ml water and dried over Na_2SO_4. Removal of the ether gave the desired alcohol (128,61g; 90%), ν_{max} 3400 cm^{-1}, δ 6,80-7,36 (m, 4H, ArH), 4,90 (t J 6Hz, 1H, 1-H), 3,82 (s, 3H, OMe), 3,16 (s, 1H, OH), 1,66-1,80 (m, 2H, 2-H), 1,20-1,48 (m, 4H, 3- and 4-H), 0,90-1,00 (m, 3H, Me).

1-(2'-methoxyphenyl)-1-pentanone

331 ml (0,663 mol) of chromic acid solution (see preparation of 1-hepten-4-one) was added to a stirred solution of 128,61g (0,663 mol) of 1-(2'-methoxyphenyl)-1-pentanol in ether (265 ml) over ½ hour, maintaining the temperature between 25 and 30°. After stirring for 2 hours at

r.t. the upper ether layer was decanted and the aqueous layer was extracted with ether. The combined ether extracts were washed successively with a 10% Na_2CO_3 solution and water, and the product was distilled to give 91,28g (0,475 mol; 71,7%) of the desired ketone, b.p.$_{13}$ 160-164^{o} (lit. b.p.$_{7}$ 142^{o} [9]), ν_{max} 1700 cm^{-1}, δ 6,90-7.70 (m, 4H, ArH), 3,90 (s, 3H, OMe), 2,98 (t J 7Hz, 2H, 2-H), 1,26-1,78 (m, 4H, 3- and 4-H), 0,94 (t J 7Hz, 3H, Me).

1-(2'-hydroxyphenyl)-1-pentanone (o-hydroxyvalerophenone)

To 25g BCl_3 (0,21 mol) in 100 ml CH_2Cl_2 kept at -10^{o} using salt and ice water was added dropwise over an hour 24g (0,125 mol) 1-(2'-methoxyphenyl)-1-pentanone in 100 ml chilled CH_2Cl_2. The colour of the solution changed from yellow to orange. The mixture was stirred at -10^{o} for 30 minutes, at r.t. for 15 minutes, and then poured onto ice. The mixture was filtered through Kieselguhr and the filtrate extracted with 2 100 ml portions of ether. The ether extracts were washed with brine and dried over Na_2SO_4. After filtering, the solution was concentrated and distilled under vacuum to yield 16,06g (0,09 mol; 72%) 1-(2'-hydroxyphenyl)-1-pentanone, b.p.$_{1,2}$ 90-92^{o} (lit. b.p.$_{0,1}$ 74^{o} [41]), ν_{max} 3500-2500, 1640 cm^{-1}, δ 12,5 (s, 1H, OH), 6,80-7,80 (m, 4H, ArH), 3,00 (t J 8Hz, 2H, 2-H), 1,28-1,84 (m, 4H, 3- and 4-H), 1,00 (t J 7Hz, 3H, Me).

Synthesis of the Phosphorus Derivatives of the Hydroxy Ketones

General Experimental Procedure

A general procedure for the preparation of these phosphorus derivatives was developed and is given below. The reaction was carried out in a 3-necked round bottomed flask which was fitted with a stirrer and a pressure equilibrating funnel. The apparatus was dried in the oven and then by gentle flaming under vacuum and was allowed to cool in a N_2 atmosphere. The organic base in the solvent to be used was placed in the flask and the phosphorus halide was added. A solution of the alcohol or ketone to be used was added dropwise with stirring at 0^o and a copious white precipitate formed. The mixture was stirred at 0^o for a further 2 or 3 hours and then left to stand overnight. The mixture was filtered under N_2 into a dry flask using a curved adaptor which was packed with glass wool. The precipitate was washed several times with small quantities of solvent. The filtrate was then concentrated under reduced pressure and filtered again under N_2 through glass wool in order to remove any amine hydrochloride which had not been removed previously. Distillation of the phosphorus derivatives was carried out under vacuum and all products were stored under N_2.

Tri(o-acetophenyl)phosphite $P(o\text{-}OC_6H_4COMe)_3$

10,23g (0,075 mol) $o\text{-}HOC_6H_4COMe$ in 50 ml ether was added to a solution of 5,93g (0,075 mol) pyridine and 3,44g (0,025 mol) PCl_3 in 130 ml ether. 4,47g crude product was obtained and was shown to be a mixture of unchanged ketone [δ 2,60 (s, Me)] and the 1,3,2-dioxaphosphorinan (25; R = $o\text{-}OC_6H_4COMe$), M^+, $^m/_e$ 300, ν_{max} 1683, 1645 cm^{-1}, δ 6,8-7,8

(m, ArH), 4,87 and 5,10 (br s $W_{\frac{1}{2}}$ 4Hz, $=CH_2$), 2,38 (s, Me). Attempted separation of the mixture by distillation yielded only a few drops of unchanged ketone, while the rest of the mixture turned into a black tar.

The reaction was repeated and the same product was obtained. 0,30g (1 mmol) $[CpFe(CO)_2I]$ and 0,420g of the mixture (≡1,4 mmol ligand) in 25 ml benzene were heated under reflux under N_2 for 60 hours; removal of the solvent gave a product, ν_{max} ($CHCl_3$) 2039, 1995, 1970 (shoulder) cm^{-1}. 0,26g (1 mmol) $[Fe_2(CO)_9]$ and 0,33g of the mixture (≡1,1 mmol ligand) in 25 ml benzene were stirred together under N_2 for 60 hours. The colour of the solution changed from orange to red-brown. The solvent was removed to give a product, ν_{max} ($CHCl_3$) 2081, 2010, 1972 cm^{-1}.

Attempted synthesis of 4-methylene-2-phenyl-5,6-benz-1,3,2-dioxaphosphorinan (25; R = Ph)

6,31g (0,05 mol) o-HOC_6H_4COMe in 70 ml ether was added to a solution of 10,12g (0,1 mol) NEt_3 and 8,95g (0,05 mol) $PhPCl_2$ in 170 ml ether. An orange liquid was isolated, ν_{max} 1618 cm^{-1}, δ 6,8-7,5 (m, ArH), 2,00 (s, Me), 1,65 (d J 20Hz, PCH_3). Crystals formed in the orange liquid but attempted isolation and purification failed.

The above reaction was repeated using benzene as solvent. A crystalline product [postulated to be (26); Scheme 31] was isolated and purified by recrystallisation from hot benzene, m.p. 182-3°, ν_{max} (nujol mull) 1618 cm^{-1}, δ 8,0-8,4 (m, 2H, ArH), 6,7-7,7 (m, 11H, ArH), 2,00 (s, 3H, Me), 1,65 (d J 20Hz, 3H, PCH_3). Found C 70,0 H 5,0; $C_{22}H_{19}O_4P$ requires C 69,83 H 5,06%; m/e 378 (M^+), 335, 259, 243, 165. Found accurate mass of 165,070 056; Ph-C-C_6H_4 requires 165,070 421; (see Scheme 31).

was distilled and 2 ml of product, b.p.$_{0,3}$ 72-76°, was isolated, δ 6,9-7,7 (m, ArH), 4,87 and 5,26 (br s $W_{\frac{1}{2}}$ 4Hz, $=CH_2$), 2,60 (s, Me of o-HOC_6H_4COMe). The same result was obtained using 500% excess PCl_3.

d) Using the ketone, NEt_3 and PCl_3 in the molar ratio of 1:2,5:2,5.

20,42g (0,15 mol) o-HOC_6H_4COMe in 150 ml ether was added very slowly with stirring to a solution of 37,92g (0,375 mol) NEt_3 and 51,52g (0,375 mol) PCl_3 in 300 ml ether. The yellow liquid (14,69g) obtained was distilled. 13,71g (45%) of the 2-chloro-1,3,2-dioxaphosphorinan (25; R = Cl) was obtained, b.p.$_{0,3}$ 72-76°, δ 6,9-7,7 (m, 4H, ArH), 4,87 and 5,26 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$). The product was stored under N_2. Any product exposed to air or moisture became red and solidified.

2-Methoxy-4-methylene-5,6-benz-1,3,2-dioxaphosphorinan (25; R = OMe)

1,92g (0,05 mol) methanol in 10 ml ether was added slowly with stirring to a solution of 2,02g (0,02 mol) NEt_3 and 4,00g (0,02 mol) compound (25; R = Cl) in 20 ml ether. 2,93g of pale yellow liquid was obtained and distilled to yield 2,56g (65%) pure product (25; R = OMe), b.p.$_{0,35}$ 64-67°. Found C 55,20 H 4,70; $C_9H_9O_3P$ requires C 55,09 H 4,63%. The observed accurate mass was 196,028 404; $C_9H_9O_3P$ requires 196,028 933, ν_{max} 3020, 2962, 2858, 1640, 1612 cm^{-1}, δ 6,9-7,8 (m, 4H, ArH), 4,74 and 5,03 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 3,62 (d J 11Hz, 3H, $POCH_3$).

2-Isopropoxy-4-methylene-5,6-benz-1,3,2-dioxaphosphorinan (25; R = OPr^i)

6,0g (0,10 mol) 2-propanol in 10 ml ether was added slowly with stirring to a solution of 3,03g (0,03 mol) NEt_3 and 6,00g (0,03 mol) compound (25; R = Cl) in 20 ml ether. 5,21g of pale yellow liquid was obtained and distilled to yield 4,36g (65%) pure product (25; R = OPr^i), b.p.$_{0,27}$ 73-78°. Found C 59,15 H 5,90; $C_{11}H_{13}O_3P$ requires C 58,91 H 5,85%. The observed accurate mass was 224,066 106; $C_{11}H_{13}O_3P$ requires

224,060 233, ν_{max} 2992, 1640, 1631, 1609 cm^{-1}, δ 6,8-7,6 (m, 4H, ArH) 4,70 and 5,03 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 4,50 (m, 1H, $-C\underline{H}Me_2$, signal collapses to a doublet, J 9Hz, on irradiation at 1,22 p.p.m.), 1,22 (t J 6Hz, 6H, Me, signal collapses to a doublet, J 6Hz, on irradiation at 4,50 p.p.m.).

4-Methylene-2-tert-butoxy-5,6-benz-1,3,2-dioxaphosphorinan (25; R = OBu^t)

7,41g (0,10 mol) 2-methyl-2-propanol in 10 ml ether was added slowly with stirring to a solution of 3,03g (0,03 mol) NEt_3 and 6,0g (0,03 mol) compound (25; R = Cl) in 20 ml ether. 4,75g of pale yellow liquid was obtained and distilled to yield 3,93g (55%) pure product (25; R = OBu^t), b.p.$_{0,20}$ 83-88°. Found C 60,90 H 6,30; $C_{12}H_{15}O_3P$ requires C 60,48 H 6,35%. The observed accurate mass was 238,076 899; $C_{12}H_{15}O_3P$ requires 238,075 833, ν_{max} 2995, 1640, 1610 cm^{-1}, δ 6,8-7,6 (m, 4H, ArH), 4,66 and 5,02 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 1,39 (s, 9H, Me).

2-Benzyloxy-4-methylene-5,6-benz-1,3,2-dioxaphosphorinan (25; R = OCH_2Ph)

6,05g (0,056 mol) benzyl alcohol in 10 ml ether was added slowly with stirring to a solution of 2,84g (0,028 mol) NEt_3 and 5,63g (0,028 mol) compound (25; R = Cl). 5,03g of crude product was isolated and was distilled to yield 2,61g (34%) pure product (25; R = OCH_2Ph), b.p.$_{0,30}$ 140-144°. Found C 66,80 H 5,10; $C_{15}H_{13}O_3P$ requires C 66,16 H 4,82%. The observed accurate mass was 272,059 609; $C_{15}H_{13}O_3P$ requires 272,062 233, ν_{max} 1650, 1620, 1502 cm^{-1}, δ 6,8-7,6 (m, 9H, ArH), 4,71 and 5,02 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 4,93 (d J 9Hz, 2H, $-O\underline{CH_2}$).

4-Methylene-2-phenoxy-5,6-benz-1,3,2-dioxaphosphorinan (25; R = OPh)

3,55g (0,0378 mol) phenol in 10 ml ether was added slowly with stirring to a solution of 3,478g (0,0344 mol) NEt_3 and 6,9g (0,0344 mol) compound (25; R = Cl) in 20 ml ether. 6,02g of crude product was isolated and was distilled to yield 5,10g (57%) pure product (25; R = OPh), b.p.$_{0,30}$ 123-127°. Found C 65,45 H 4,30; $C_{14}H_{11}O_3P$ requires C 65,11 H 4,30%. The observed accurate mass was 258,045 467; $C_{14}H_{11}O_3P$ requires 258,044 583, ν_{max} 1644, 1611, 1600, 1500 cm^{-1}, δ 6,9 - 7,8 (m, 9H, ArH), 4,82 and 5,12 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$).

Reaction of the 1,3,2-dioxaphosphorinans (25; R = OMe, OPh) with HCl gas.

Dry HCl gas was generated by adding concentrated HCl dropwise to concentrated H_2SO_4 and passing the gas formed through concentrated H_2SO_4. The dry HCl was bubbled through a solution of compound (25; R = OMe) in [^{2}H]-$CHCl_3$. The peaks due to the exocyclic methylene protons disappeared and a singlet appeared at δ 2,60 due to the acetyl group of o-HOC_6H_4COMe (ν_{max} 1645 cm^{-1}). The same results were obtained when dry HCl gas was bubbled through a solution of (25; R = OPh).

2-Chloro-4-propylidene-5,6-benz-1,3,2-dioxaphosphorinan (27; R = Cl)

9,85g (0,06 mol) o-$HOC_6H_4COC_3H_7$ in 100 ml ether was added slowly with stirring to a solution of 15,17g (0,15 mol) NEt_3 and 20,61g (0,15 mol) PCl_3 in 200 ml ether. 10,30g of crude product was obtained δ 6,9-7,7 (m, 4H, ArH), 5,72 (t J 7Hz, 1H, =CH, this triplet was further split by coupling to phosphorus, J 2Hz), 2,29 (pent J 7Hz, 2H, CH_2CH_3), 1,07 (t J 7Hz, 3H, Me). This product was used in subsequent

reactions without purification since decomposition occurred on distillation.

2-Methoxy-4-propylidene-5,6-benz-1,3,2-dioxaphosphorinan (27; R = OMe)

2,88g (0,09 mol) methanol in 10 ml ether was added dropwise with stirring to a solution of 4,55g (0,045 mol) NEt_3 and 10,3g (0,045 mol) compound (27; R = Cl) in 20 ml ether. 6,74g of crude product was isolated and distilled to yield 5,62g (55%) pure compound (27; R = OMe), b.p.$_{0,27}$ 93-98°. Found C 59,20 H 5,80; $C_{11}H_{13}O_3P$ requires C 58,91 H 5,85%. The observed accurate mass was 224,059 537; $C_{11}H_{13}O_3P$ requires 224,060 233, ν_{max} 2980, 2950, 1660, 1610, 1578 cm^{-1}, δ 6,8-7,5 (m, 4H, ArH), 5,48 (t J 7Hz, 1H, =CH, this triplet was further split by coupling to phosphorus, J 2Hz), 3,60 (d J 11Hz, 3H, $POCH_3$), 2,32 (pent J 7Hz, 2H, $\underline{CH_2}CH_3$), 1,07 (t J 7Hz, 3H, Me).

2-Chloro-6-methyl-4-methylene-1,3,2-dioxaphosphorinan (29; R = Cl)

10,01g (0,10 mol) 2,4-pentanedione in 100 ml ether was added dropwise with stirring to a solution of 20,22g (0,20 mol) NEt_3 and 27,48g (0,20 mol) PCl_3 in 200 ml ether. The crude product was purified by distillation and 3,32g (20%) product (29; R = Cl) was obtained, b.p.$_{0,35}$ 28-38°, δ 5,50 (d J 3Hz, 1H, 5-H), 4,35 and 4,50 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 1,92 (s, 3H, Me). Due to the labile nature of the compound full characterisation could not be carried out.

2-Methoxy-6-methyl-4-methylene-1,3,2-dioxaphosphorinan (29; R = OMe)

1,96g (0,04 mol) methanol in 10 ml ether was added dropwise with stirring to a solution of 2,02g (0,02 mol) NEt_3 and 3,32g (0,02 mol)

compound (29; R = Cl) in 20 ml ether. The crude product was purified by distillation and a few drops of product (29; R = OMe) were obtained, b.p.$_{0,55}$ 23°, M^+, $^m/_e$ 160, δ 5,38 (d J 3Hz, 1H, 5-H), 4,12 and 4,34 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 3,65 (d J 11Hz, 3H, OMe), 1,90 (s, 3H, Me). This product was very unstable and solidified even when stored under N_2.

Attempted synthesis of 4-methylene-2-phenoxy-5,6-benz-1,3,2-dioxaphosphorinan (25; R = OPh) using $PhOPCl_2$

The $PhOPCl_2$ used was prepared from phenol and PCl_3 according to the method of Tolkmith[62]. 6,82g (0,05 mol) o-HOC_6H_4COMe in 90 ml ether was added dropwise with stirring to a solution of 10,12g (0,10 mol) NEt_3 and 9,8g (0,05 mol) $PhOPCl_2$ in 200 ml ether. 6,2g of crude product was obtained, ν_{max} 1645 cm^{-1}, δ 6,80-7,72 (m, 9H, ArH), 4,88 and 5,12 (br s $W_{\frac{1}{2}}$ 4Hz, 2H, $=CH_2$), 2,6 (s, 3H, Me). Crystals which formed in the crude product could not be purified and characterised.

o-Acetophenyl diphenylphosphinite [Ph_2P(o-OC_6H_4COMe)]

6,82g (0,05 mol) o-HOC_6H_4COMe in 90 ml ether was added dropwise with stirring to a solution of 5,56g (0,055 mol) NEt_3 and 11,11g (0,055 mol) Ph_2PCl in 200 ml ether. 7,12g of crude product was obtained and was shown to be a mixture of 25% unreacted ketone and 75% desired product, ν_{max} 1683, 1645 cm^{-1}, δ 6,62-7,70 (m, ArH), 2,60 (s, Me of o-HOC_6H_4COMe) 2,40 (s, Me of Ph_2P(o-OC_6H_4COMe)). Fractional distillation failed to separate the components of the mixture.

0,31g (1,0 mmol) [$CpFe(CO)_2I$] and 0,47g of the above mixture (≡ 1,1 mmol ligand) were dissolved in 30 ml benzene and stirred under

nitrogen for 60 hours. The solution became green and was heated under reflux for 3 hours. The solvent was removed to give a product, ν_{max} ($CHCl_3$) 2039, 1995, 1972 cm^{-1}. 0,26g (1 mmol) [$Fe_2(CO)_9$] and 0,47g of the above mixture (≡ 1,1 mmol ligand) in 25 ml benzene were stirred under nitrogen for 60 hours. The colour of the solution changed from orange-red to brown. Removal of the solvent gave a product, ν_{max} ($CHCl_3$) 2061, 1990, 1952 cm^{-1}.

Repetition of the reaction using o-HOC_6H_4COMe and Ph_2PCl in the molar ratio of 1 : 1,5 also resulted in the isolation of a mixture of products consisting of 25% o-HOC_6H_4COMe and 75% of the desired product. Once again it was not possible to separate the two components of the mixture. Fractional distillation yielded mixtures containing the two products in varying amounts.

Attempted synthesis of 2-(o-acetophenoxy)-4,5-benz-1,3,2-dioxaphosphorolan (33; R = Me)

o-Phenylene phosphorochloridite was prepared from catechol and PCl_3 according to the literature procedure[28]. 5,45g (0,04 mol) o-HOC_6H_4COMe in 35 ml ether was added dropwise with stirring to a solution of 4,05g (0,04 mol) NEt_3 and 6,96g (0,04 mol) o-phenylene phosphorochloridite in 120 ml ether. 4,86g of crude product was isolated and consisted of 30% unreacted ketone and 70% of the desired product (33; R = Me), ν_{max} 1680, 1645 cm^{-1}, δ 6,86-7,70 (m, ArH), 2,60 (s, Me of o-HOC_6H_4COMe), 2,52 (s, Me of 33; R = Me). An attempt to separate the components by fractional distillation failed; 0,5g unreacted ketone was recovered and the rest of the mixture turned into a tar.

Repetition of the reaction using o-HOC_6H_4COMe and o-phenylene phosphorochloridite in the molar ratios of 1 : 1,1, 1: 1,5 or 1 : 2 also resulted in the isolation of mixtures containing the unreacted ketone and the desired product. Attempts to separate this mixture were unsuccessful.

Attempted synthesis of 2-(o-butyrophenoxy)-4,5-benz-1,3,2 dioxaphosphorolan (33; R = Pr^n)

5,8g (0,035 mol) o-$HOC_6H_4COC_3H_7$ in 35 ml ether was added dropwise to a solution of 7,08g (0,07 mol) NEt_3 and 12,18g (0,07 mol) o-phenylene phosphorochloridite in 120 ml ether. 11,09g of crude product consisting of a mixture of unreacted ketone and the desired product (33; R = Pr^n) was obtained, ν_{max} 1682, 1645 cm^{-1}. The two components of the mixture could not be separated by fractional distillation.

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